MODELING OF SYSTEMIC INFLAMMATORY RESPONSE TO INFECTION

CROSS-REFERENCE TO RELATED APPLICATION

This application claims priority to U.S. Provisional Application No. 60/523,296, the disclosure of which is incorporated by reference herein.

FIELD OF THE INVENTION

This invention relates to models for the systemic inflammatory response to infection comprising immunocomprised mice. The invention also relates to methods of using the models to identify biomarkers correlated with the systemic inflammatory response to infection, to identify biomarker panels useful in staging the disease, and to predict disease outcome. Further, the invention relates to methods for evaluating potential treatments for sepsis.

BACKGROUND OF THE INVENTION

Septic shock is among the leading causes of death of hospitalized patients and is a condition for which insufficient treatment options are available. The search for new effective treatments for sepsis has been limited. The incidence of sepsis is expected to increase sharply in the near future due to aging of the population, advances in technology, widespread use of new medical devices, and the advent of procedures that extend survival of critically ill patients. The incidence of sepsis has been increasing in the last 20 years and current figures indicate the presence of 750,000 cases per year of severe sepsis in the United States alone (Angus, D. C. *et al.* Crit. Care Med. 29:1303-1310, 2001). The estimated crude mortality is 35%, all comorbidities being considered (Rangel-Frausto, M S. Infectious Disease Clinics of North America 13(2):299-312, 1999). Sepsis is the 10th leading cause of death in the United States, and among hospitalized patients in noncoronary intensive care units, has been reported to be the most common cause of death. The disease accounts for an estimated $16 billion in annual health care expenditures in the United States alone.

During bacterial infections, bacteria and its products can cause septic shock that can result in death. For example, endotoxins are usually heat-stable lipopolysaccharide-protein complexes of high toxicity, typically formed by gram-negative bacteria, *e.g.*, of the genera Brucella, Haemophilus, Escherichia, Klebsiella, Proteus, Salmonella, Pseudomonas, Shigella, Vibrio, Yersinia. Septic shock is often associated with bacteremia due to gram-negative bacteria or meningococci. Pathogen species which cause sepsis include bacterium species, *e.g.*, a bacterium species selected from the group consisting of Enterococcus spp.,

Staphylococcus spp., Streptococcus spp., Enterobacteriacae family, Providencia spp., Pseudomonas spp. and others. Sepsis and its consequences, severe sepsis and septic shock can result from Gram negative, Gram positive bacteria, fungi and viruses.

The terms sepsis, bacteremia and septicemia have been used interchangeably in the past; however, approximately one of every three patients presenting with sepsis have sterile cultures, indeterminate microbiological studies or lack a definite site of infection. Therefore, sepsis is now considered to be the clinical presentation of patients with a serious infection, who demonstrate a systemic inflammatory response to infection that may or may not be accompanied by a positive blood culture. Severe sepsis, the most common type found in the intensive care unit (ICU), is the systemic inflammatory response induced by infection and accompanied by evidence of altered organ function or perfusion. Sepsis, including all stages through septic shock, results from the inability of the immune system to properly control a bacterial infection. Upon interaction with microbial components, cells of the immune system initiate an inflammatory response aimed at avoiding a systemic infection and promoting clearance of the bacteria. In some instances, however, bacteria gain access to the circulation, resulting in mis-regulated production of inflammatory cytokines, sepsis syndrome, septic shock, and eventually death. Descriptions for the stages of sepsis are set forth in Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, Cohen J, Opal SM, Vincent JL, Ramsay G. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference, Crit. Care Med 2003;31:1250-6, and in the preceding conference held in 1991 and described in the 1992 report, Bone RC et al., American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, Chest 101:1644-1655, which describe sepsis as a clinical syndrome defined by the presence of both infection and a systemic inflammatory response.

Sepsis is a systemic inflammatory response to infection. Three major stages have been put forth by the Consensus Conference of the American College of Chest Physicians and by the Society of Critical Care Medicine. The first stage, Systemic Inflammatory Response Syndrome (SIRS), requires two or more of the following conditions: fever or hypothermia, tachypnea, tachycardia, leukocytosis, and leukopenia. In the second stage, sepsis proceeds to a more severe complication called "severe sepsis" or "sepsis syndrome," which is sepsis with one or more signs of organ dysfunction (for example, metabolic acidosis, acute encephalopathy, oliguria, hypoxemia, or disseminated intravascular coagulation) or

hypotension. Finally, in the third stage, septic shock, in which hypotension that is unresponsive to fluid resuscitation along with organ dysfunction occurs, is observed.

Staging sepsis to identify points at which the clinician can intervene with preventive measures has been and continues to be a very challenging task. Broad disease definitions have limited the ability of clinicians to identify appropriate therapies for patients who have sepsis and who are at high risk for developing sepsis. In addition, these definitions do not permit the clinician to differentiate between an at-risk patient who may derive a net benefit from a new therapy and a patient who will either not benefit, given his/her underlying disease co-morbidities, or who may be placed at higher risk from the therapy's inherent safety profile. Additionally, the variability of disease progression and sequelae have made staging sepsis very difficult. Furthermore, certain treatments have been found to have opposite effects on sepsis patients depending on when they are administered. For example, therapies directed against TNF-α have been shown to both worsen and improve survival in patients with sepsis. Such results are speculated to be due to a change in the syndrome over time, with initial sepsis characterized by increases in inflammatory mediators, but with a later shift toward an antiinflammatory immunosuppressive state (Hotchkiss *et al.*, "The Pathophysiology and Treatment of Sepsis," The New England Journal of Medicine 348:2, Jan. 9, 2003). The difficulty in staging sepsis, combined with the contrasting results obtained with treatments tested, have made it very difficult to identify candidate drugs for treating sepsis and sepsis syndrome.

There are scoring systems and predictive models for sepsis, and general disease scoring systems that have been applied to sepsis. These scoring systems include the Injury Severity Score (ISS, 1974) which is a measure of the severity of blunt trauma injury to five major body systems; the Glasgow Coma Scale (SCS, 1974) which measures mental status changes; the Trauma Score (1980), which extends the Glasgow score to include respiratory and hemodynamic parameters; the TRISS method, which combines physiologic and anatomic measurements to assess probability of surviving an injury; the Sepsis Severity Score (1983), which grades the functioning of seven body organs; the Polytrauma Score (1985), which adds an age parameter to the Injury Severity Score; the Multiple Organ Failure (MOF) Score (1985), which assesses the function of seven major organ systems; and the APACHE II (1985). The APACHE II is a scoring system that utilizes data from routinely measured physiological assessments in addition to a general health status score and an age score (reviewed by Roumen, R L *et al.*, J. Trauma 35: 349-355, 1993). APACHE II, and its more

recent version APACHE III, are used to evaluate how sick an individual is, rather than to diagnose sepsis.

Various pro-inflammatory cytokines are associated with sepsis. Use of measurements of one or more pro-inflammatory cytokine to evaluate the severity of inflammation in patients with SIRS has been reported. Takala, A. *et al.* (Clin. Sci. 96, 287-295 [1999]) described measuring levels of a small group of analytes - CD11b, IL-6, IL-1β, TNF-α, and C-reactive protein groups - in SIRS patients meeting two, three, or four SIRS criteria. Based on their measurement of the markers, the authors used a whole number subscore, known as the Systemic Inflammation Composite Score (SICS), to compare the severity of inflammation in the patients. They concluded that their results suggest that if the SICS is low, an acutely ill patient who meets the SIRS criteria most probably does not have sepsis, whereas if the SICS is high, the patient should be carefully examined for the presence of infection, among other disorders able to elicit the systemic inflammatory reaction.

U.S. Patent No. 6,190,872 describes measurement of acute inflammatory response mediators known or suspected to be involved in the inflammatory response to identify patients at risk for developing a selected systemic inflammatory condition prior to development of signs and symptoms which are diagnostic of the selected systemic inflammatory condition.

U.S. Patent No. 5,804,370 describes a method for determining the presence or extent of sepsis in a human or animal patient using an antibody assay to determine the amount of an analyte, including TNF, IL-1, IL-6, IL-8, Interferon and TGF-β. These analytes have been shown not to be necessarily predictive of survival vs. death.

Published Application No. US2003/0194752 describes a method for detecting early sepsis using a statistical measure of the extreme values of analyte measurements obtained over time, rather than a statistical analysis of values of analytes obtained from samples at a selected timepoint.

Billions of dollars have been spent to generate treatments to prevent a fatal outcome for sepsis/septic shock. Such efforts have been largely unsuccessful--an alarming result for a disease syndrome with a current mortality rate of 30 to 50%. Moreover, the incidence of sepsis/septic shock is expected to steadily increase, reflecting an aging population and advancing technologies that prolong survival of immunocompromised and critically ill patients. Despite the efforts made to develop treatments, there is just one approved drug, which is indicated for only the most severe cases of septic shock. Furthermore, even with

respect to that drug, Xigris® (Lilly), there is not a straightforward way to determine when the drug should be administered to a sepsis patient.

Animal models for use in research have also been described. U.S. Patent No. 6,368,572 describes a chimeric hematopoietic-deficient mouse as a model for toxin shock. U.S. Patent No. 6,610,503 describes a method for predicting an expected time of death of an experimental animal in a model system of sepsis using data generated in the initial part of the experiment.

Obstacles for developing sepsis therapies include incomplete understanding of the syndrome, inadequacies in staging the syndrome, and lack of adequate animal models. Currently, animal models for sepsis syndrome do not mimic the human disease and have been considered an important cause behind the failure of proposed therapies. Murine models have been used extensively with limited success to evaluate the efficacy of therapeutics in development for septic shock. Analysis of these models has revealed that two major important differences exist in the progression of the disease in humans compared to the disease in mice that may explain the unreliability of prior murine models to predict future clinical success. The first major difference is that generally young, healthy animals are used in the murine models, whereas sepsis syndrome typically occurs in critically ill patients, or patients whose immune defenses are impaired (either by trauma, surgery or severe burns, or by immunocompromising disorders, such as cancer and chemotherapy). The second major difference concerns the establishment of the septic state in murine models (*e.g.*, the agent, the route, and the mode of challenge). In the majority of murine models, healthy animals typically receive a bolus dose of either LPS or live microorganisms intravenously or intraperitoneally and will develop septic shock and achieve a moribund state within 24 hours. In septic human patients, the source and identity of the triggering infection is not always apparent and patients develop septic shock and die after a period of several days. Moreover, the SICS scoring system and other scoring systems have not provided effective modeling to predict outcome or to detect when and if a given patient has become septic.

Thus, there is a need for more predictive or accurate models of sepsis. An animal model that more closely resembles the human disease would more closely predict the efficacy of potential drug targets and the outcome of potential therapies.

SUMMARY OF THE INVENTION

General aspects of the invention are defined in the appended independent claims, which for the sake of brevity are incorporated by reference herein. Preferred embodiments of the invention are defined in the dependent claims following the detailed description, which are likewise incorporated by reference herein. Other preferred embodiments as well as exemplary features and advantages of the invention will become apparent from the detailed description taken in conjunction with the drawing figures.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A-1C show the time-profiles of the measured concentrations of the 57 analytes assayed in INFECTED mice (solid lines) vs. XR.INFECTED mice (dotted lines). The analyte names are listed on the Y-axis. Concentration values are in picograms per milliliter (pg/ml). The two-way ANOVA interaction p value for each analyte is listed above each graph. Error bars represent one standard deviation above or below the mean at a given time point.

Figures 2A-2D show plots of the log2-transformed data depicted in Figures 1A-1C. All the measurements are plotted as points and the mean time-profiles are represented in *lowess*-fitted lines (Cleveland, W. S. (1979), "Robust locally weighted regression and smoothing scatterplots," *J. Amer. Statist. Assoc.* Vol. 74, pp. 829-836). The dotted curves represent data derived from XR.INFECTED mice.

Figures 3A-3E show the time-profiles of the 28 analytes depicted in Figures 1A-1C that displayed a two-way ANOVA interaction p value < 0.1. Error bars represent 1 standard deviation above or below the mean at a given time point. The analyte names are listed on the Y-axis. Concentration values are presented in picograms per milliliter (pg/ml). The two-way ANOVA interaction p value for each analyte is listed above each graph. The dotted curves represent data derived from XR.INFECTED mice.

Figure 4 shows box-and-whisker plots of analyte measurements taken at 4 hours and zero hour that showed an interaction p value < 0.05. The boxes are drawn with widths proportional to the square-roots of the number of observations in the groups, and a notch is drawn in each side of the boxes. Notches of two plots that do not overlap reflect a substantial difference between the medians of such plots (Chambers, et al., Graphical Methods for Data Analysis, Wadsworth & Brooks/Cole (1983)).

Figure 5 shows box-and-whisker plots of analyte measurements taken at 4 hours and zero hour that showed an interaction p value < 0.05. Boxes are rendered as described for Figure 4.

Figure 6 shows box-and-whisker plots of analyte measurements taken at 4 hours and zero hour that showed an interaction p value < 0.05. Boxes are rendered as described for Figure 4.

Figure 7 shows box-and-whisker plots of analyte measurements taken at 4 hours and zero hour that showed an interaction p value < 0.05. Boxes are rendered as described for Figure 4.

Figure 8 shows box-and-whisker plots of analyte measurements taken at 4 hours and zero hour that showed an interaction p value < 0.05. Boxes are rendered as described for Figure 4.

Figure 9 shows box-and-whisker plots of analyte measurements taken at 4 hours and zero hour that showed an interaction p value < 0.05. Boxes are rendered as described for Figure 4.

Figure 10 shows a Kaplan-Meier curves comparing survival rates derived from irradiated mice treated with one dose every 24 hours post-infection for four days of ethyl pyruvate ("EP") at 35 mg/ml, eight doses of ethyl pyruvate ("EP2x") at 35 mg/ml at 24, 30, 48, and 54 hours post-infection and every 24 hours thereafter for four days, four doses of ceftriaxone (CEF) at 0.1 mg/ml every 24 hours post-infection for days, and untreated animals ("Control"). Arrows denote 24, 48, 72, and 96 hour dosage times.

Figure 11 shows median VEGF concentration from INFECTED (solid line and x's) and XR.INFECTED (dotted line and circles) mice measured at the indicated time points. VEGF concentration units are pictogram per milliliter (pg/ml).

Figures 12A-12D show Kaplan-Meier curves (figures 12A and 12C) and box-and-whisker plots (Figures 12B and 12D) comparing survival rates derived from irradiated mice treated with anti-VEGF antibody ("anti-VEGF") and anti-VEGF antibody isotype control ("control"). Figures 12A and 12B compare data derived from all animals in the experiment. Figuers 12C and 12D exclude data derived from animals with bacterial counts $>10^4$.

Figures 13A-13D show Kaplan-Meier curves (figures 13A and 13C) and box-and-whisker plots (Figures 13B and 13D) comparing survival rates derived from irradiated mice treated with anti-VEGF antibody ("anti-VEGF") and anti-VEGF antibody isotype control

("control"). Figures 13A and 13B compare data derived from all animals in the experiment. Figuers 13C and 13D exclude data derived from animals with bacterial counts $>10^4$.

Figures 14A-14D show plots of the combined data derived from ceftriaxone-treated animals used in the experiments performed to generate the data depicted in Figures 12A-13D. The survival difference between the combined "control" and "treatment" groups is depicted in Figure 14A. There is no difference in terms of bacterial count (Figure 14B) and health between the two groups. Figures 14C and 14D show similar plots, but which exclude animals with bacterial counts $>10^4$.

Figures 15A-15D shows plots of the combined data from all animals used in the experiments performed to generate the data depicted in Figures 12A-13D. The survival difference between the combined "control" and "treatment" groups is depicted in Figure 15A. There is no difference in terms of bacterial count (Figure 15B) and health between the two groups. Figures 15C and 15D show similar plots, but which exclude animals with bacterial counts $>10^4$.

Figures 16A-16D show Kaplan-Meier curves (figures 16A and 16C) and box-and-whisker plots (Figures 16B and 16D) comparing survival rates derived from irradiated mice treated with anti-VEGF antibody ("anti-VEGF") and anti-VEGF isotype control ("control"). Figures 16A and 16B compare data derived from all animals in the experiment. Figures 16C and 16D exclude data derived from animals with bacterial counts $>10^4$.

Figures 17A-17D show Kaplan-Meier curves (figures 17A and 17C) and box-and-whisker plots (Figures 17B and 17D) comparing survival rates derived from irradiated mice treated with anti-VEGF antibody ("anti-VEGF") and anti-VEGF isotype control ("control"). Figures 17A and 17B compare data derived from all animals in the experiment. Figures 17C and 17D exclude data derived from animals with bacterial counts $>10^4$.

Figures 18A-18D show plots of the combined data from animals that received anti-VEGF antibody or anti-VEGF isotype control used in the experiments performed to generate the data depicted in Figures 16A-17D. The survival difference between the combined "control" and "treatment" groups is depicted in Figure 18A. There is no difference in terms of bacterial count (Figure 18B) and health between the two groups. Figures 18C and 18D show similar plots, but which exclude animals with bacterial counts $>10^4$.

Figures 19A-19B shows plots of the combined data for all animals used in the experiments performed to generate the data depicted in Figures 16A-17D. The survival difference between the combined "control" and "treatment" groups is depicted in Figure

18A. There is no difference in terms of bacterial count (Figure 18B) and health between the two groups. Figures 18C and 18D show similar plots, but which exclude animals with bacterial counts $>10^4$.

Figure 20 shows the median JE/MCP-1 concentration from INFECTED (solid line and x's) and XR.INFECTED (dotted line and circles) mice measured at the indicated time points. VEGF concentration units are pictogram per milliliter (pg/ml).

Figures 21A-21X show Kaplan-Meier curves (Figures 21A-21D, 21I-21L, and 21Q-21T) and box-and-whisker plots (Figures 21E –21H, 21M-21P, and 21U-21X) comparing survival rates derived from irradiated mice treated with anti-JE/MCP-1 antibody ("antiJE") and anti-JE/MCP-1 isotype control ("ISO"). The survival difference between groups A, B, and C (described in Example 8) is depicted in Figure 21A. The survival difference between groups A and C is depicted in Figure 21B. The survival difference between groups A and B is depicted in Figure 21C. The survival difference between groups B and C is depicted in Figure 21D. There is no difference in terms of bacterial count and health between the three groups, as seen in Figures 21E-21H. Figures 21I-21L show similar plots, but which exclude animals with bacterial counts $>10^4$. The survival difference between groups A, B, and C is depicted in Figure 21I. The survival difference between groups A and C is depicted in Figure 21J. The survival difference between groups A and B is depicted in Figure 21K. The survival difference between groups B and C is depicted in Figure 21L. There is no difference in terms of bacterial count and health between the three groups, as seen in Figures 21M-21P. Figures 21Q-21X show plots of data from animals used in the experiment that did not die and were not euthanized before the second treatment. The survival difference between groups A, B, and C is depicted in Figure 21Q. The survival difference between groups A and C is depicted in Figure 21R. The survival difference between groups A and B is depicted in Figure 21S. The survival difference between groups B and C is depicted in Figure 21T. There is no difference in terms of bacterial count and health between the three groups, as seen in Figures 21U-21X.

Figures 22A-22F show Kaplan-Meier curves (Figures 22A, 22C, and 22E) and box-and-whisker plots (Figures 22B, 22D, and 22F) comparing survival rates derived from irradiated mice treated with anti-JE/MCP-1 antibody ("antiJE") and anti-JE/MCP-1 isotype control ("ISO"). The survival difference between groups A and B (described in Example 8) is depicted in Figure 22A. There is no difference in terms of bacterial count and health between the two groups, as seen in Figures 22B. Figure 22C shows a similar plot, but which

excludes animals with bacterial counts $>10^4$. There is no difference in terms of bacterial count and health between the two groups, as seen in Figure 22D. The survival difference between groups A and B, excluding animals that were euthanized before ceftriaxone treatment, is depicted in Figure 22E. There is no difference in terms of bacterial count and health between the three groups, as seen in Figure 22F.

Figures 23A-23F show Kaplan-Meier curves (Figures 23A, 23C, and 23E) and box-and-whisker plots (Figures 23B, 23D, and 23F) comparing survival rates derived from the combined data from animals used in the experiments performed to generate the data depicted in Figures 21A-22F. Figure 23A shows the survival difference between "ISO" and "antiJE" groups. There is no difference in terms of bacterial count (Figure 23B) and health between the two groups. Figures 23C and 23D show similar plots, but which exclude animals with bacterial counts $>10^4$. Figures 23E-23F show plots of the combined data for all animals used in the experiment that did not die and were not euthanized before the second treatment.

Figures 24A-24F show Galaxy maps for five different groups of analytes analyzed by PCA as indicated above each Figure. The solid line in each Figure denotes a plane that is discerned, which separates data points derived from Survived animals, which fall generally on the left side of each line in each map, and Doomed animals, which fall generally on the right side of each line in each map. Numbers in each map represent the number of animals that were misclassified by the PCA of each respective group of analytes.

Figures 25A-25B show Kaplan-Meier curves comparing survival rates derived from irradiated and untreated mice to the survival rates of irradiated mice that were subsequently treated with either one of the VEGF antagonists, Compounds I and II.

Figure 26 shows Kaplan-Meier curves comparing survival rates derived from irradiated and untreated mice to the survival rates of irradiated mice that were subsequently treated with either 50 μg/ml rosiglitazone or 200 μg/ml rosiglitazone.

DETAILED DESCRIPTION OF THE INVENTION AND ITS PREFERRED EMBODIMENTS

The present invention provides methods for using an immunocompromised animal model to study the systemic inflammatory response to infection, including selecting panels of biomarkers used for staging sepsis syndrome in animal subjects, including humans, and for predicting disease outcomes in these subjects. The invention further provides methods for using the biomarker panels to identify candidate drugs for treatment of sepsis and sepsis syndrome. The invention can also be used to identify new biomarkers correlated with sepsis from analytes identified in proteomic and genomic studies. The invention provides methods

for determining reference scores for a group of immunocompromised infected animals in a model system, and methods for using the animal models to validate drug targets and to test therapeutic compounds.

The invention also relates to methods for selecting a panel of biomarkers useful for determining the stage of sepsis syndrome in an animal species comprising: providing a plurality of biological samples taken at a selected timepoint or timepoints, the samples selected from at least two groups of animals where the first group comprises survived immunocompromised individuals infected by a sepsis-causing pathogen and the second group comprises doomed immunocompromised individuals infected by a sepsis-causing pathogen; measuring the amount of each of a plurality of analytes in the biological samples from each group and generating a dataset for each group; and performing an analysis, for example, a statistical analysis, on the data. The statistical analysis can comprise conducting a univariate statistical test on the dataset, for each analyte, to compare the dataset for biological samples from the first group to the dataset for biological samples from the second group of animals. Further, analytes can be selected according to their significance level as determined by the univariate statistical test.

The invention provides using the univariate statistical analysis to identify those analytes that are associated with a given outcome at a desired significance level, *e.g.*, 0.05 or better (*e.g.*, 0.04, 0.03, 0.02, or 0.01). A significance level of 0.05 is a standard typically used in statistical research. Depending on the purpose of the research, the statistical stringency can be lowered to 0.02, 0.01 or even smaller.

Univariate statistical analyses include the T-test. The T-test is a statistical method to test the equality of means of the two groups of biological samples that are being compared. There are many univariate statistical tests available for use in different situations and for different purposes, including the nonparametric Wilcoxon two sample test, analysis of variance (ANOVA), and other univariate statistical tests known to statisticians and biostaticians.

The invention further provides transforming the data obtained for each group of animals or individuals to log scale. Generally, transforming the data to log scale renders the distribution of the data close to normal distribution, thus making the statistical tests used advantageous because most statistical tests either require normal distribution or would be optimal under normal distribution.

The present invention additionally provides methods of selecting a panel of biomarkers as described above, further comprising the step of deriving a discrimination function for the selected biomarkers, where the deriving comprises performing a principle component analysis and a linear discriminant analysis, and where the discrimination function can be used to generate a score for each animal.

In one embodiment of the invention, the analytes tested include (but are not limited to): Apolipoprotein A1, β2 Microglobulin, C Reactive Protein, D-dimer, EGF, Endothelin-1, Eotaxin, Factor VII, FGF-9, FGF-Basic, Fibrinogen, GCP-2, LIX, GM-CSF, Growth Hormone, GST, Haptoglobin, IFN-γ, IgA, IL-10, IL-11, IL-12p70, IL-17, IL-18, IL-1α, IL-1ß, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, Insulin, IP-10, KC-GRO, Leptin, LIF, Lymphotactin, monocyte chemoattractant protein 1 (MCP-1 or JE), MCP-3, MCP-5, M-CSF, MDC, MIP-1α, MIP-1ß, MIP-1α, MIP-2, MIP-3ß, Myoglobin, OSM, RANTES, SCF, SGOT, TIMP-1, Tissue Factor, TNF-α, TPO, VCAM-1, VEGF, and VWF. In other embodiments of the invention, the selected panel of biomarkers includes MCP-1-JE, IL-6, MCP-3, IL-3, MIP-1ß, and KC-GRO, and the discrimination function is represented as 19(MCP-1-JE) + 27(IL-6) + 18(MCP-3) + 21(IL-3) + 18(MIP-1ß) + 25(KC-GRO).

Preferred panels of biomarkers therefore include: (i) Apolipoprotein A1, β2 Microglobulin, C Reactive Protein, D-dimer, EGF, Endothelin-1, Eotaxin, Factor VII, FGF-9, FGF-Basic, Fibrinogen, GCP-2, LIX, GM-CSF, Growth Hormone, GST, Haptoglobin, IFN-γ, IgA, IL-10, IL-11, IL-12p70, IL-17, IL-18, IL-1α, IL-1ß, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, Insulin, IP-10, KC-GRO, Leptin, LIF, Lymphotactin, MCP-1-JE, MCP-3, MCP-5, M-CSF, MDC, MIP-1α, MIP-1ß, MIP-1α, MIP-2, MIP-3ß, Myoglobin, OSM, RANTES, SCF, SGOT, TIMP-1, Tissue Factor, TNF-α, TPO, VCAM-1, VEGF, and VWF; or (ii) MCP-1-JE, IL-6, MCP-3, IL-3, MIP-1ß, and KC-GRO. Other preferred biomarker panels comprise at least MCP-1, more preferably MCP-1 and VEGF. Such biomarkers may be used to provide a sepsis diagnosis or survival prognosis or to monitor the efficacy of a treatment, e.g., in a clinical setting.

In the methods of the invention, exemplary animal species include humans and other mammals, including mice, rabbits, monkeys, dogs and birds. In one embodiment, the invention provides for analyzing a biological sample at a timepoint of 22 hours following infection with a pathogen species, but the invention also provides for analysis of biological samples at timepoints taken throughout the course of disease, at death, and following

recovery from the disease. The invention provides for the use of blood, serum or other body fluids, including blood plasma, cerebrospinal fluid, lymph aspirate, bronco-alveolar lavage, ascitis and essudates obtained from the infection site, and tissues, including homogenized organs.

The invention also provides for the selection of a panel consisting of biomarkers determined to be characteristic of a disease stage. This determination can be based on the statistical analysis of the analyte levels measured in diseased and control animals. In certain embodiments, the panel consists of fifteen or fewer biomarkers, or ten or fewer biomarkers, or five or fewer biomarkers, e.g., nine, eight, seven, six, four, three, two or one biomarker, but is not limited to those number of biomarkers.

The invention additionally permits for using OmniViz Analysis® software (OmniViz, Inc., Maynard, MA), or an equivalent or similar data-visualization application, to evaluate the ability of a biomarker panel to discriminate different groups, i.e., to predict disease outcome. The OmniViz software employs a "Galaxy" visualization approach to pattern and relationship determination among data. In a Galaxy visualization, each data point is represented, and the data are logically grouped into sets or clusters of similar data, with an open circle associated with each cluster reflecting the mathematical centroid for the data in the cluster. Proximity of points represents relatedness, and therefore facilitates analysis and interpretation of data.

The present invention also provides methods for staging sepsis and sepsis syndrome and predicting survival using an immunocompromised animal model system. More particularly, the invention provides a method for predicting whether an animal with sepsis syndrome will survive or die, comprising: providing a biological sample from an animal suspected of being infected by a sepsis-causing pathogen; providing a panel of biomarkers useful for determining the stage of sepsis syndrome in the animal species, the panel selected according to methods of the invention as described herein; measuring, in the biological sample, the amount of the biomarkers; generating a score for the biological sample using the discrimination function determined; and comparing the score with at least one score determined using a biological sample from a survived immunocompromised animal and at least one score determined using a biological sample from a doomed immunocompromised animal.

Patients in different stages of sepsis may not be responsive to a given treatment, if that treatment is not effective when administered during some stages of sepsis. Methods according to the invention are useful for characterizing stages of the disease useful for

studying the effectiveness of drugs for treating sepsis, severe sepsis and septic shock as well as for investigating the cellular and molecular mechanisms important in sepsis. This can be accomplished through comparing data obtained for a panel in a diseased biological sample with data obtained using the same panel in an uninfected control biological sample. The information obtained can be used to stage disease in a test biological sample. The invention further permits screening a compound or molecular entity for its efficacy as a potential drug or treatment for sepsis using the methods of the invention.

Methods of the invention employ an immunocompromised animal model for staging sepsis syndrome in the animal. Certain embodiments of the method comprise: providing a biological sample from an animal suspected of being infected by a sepsis-causing pathogen; and providing a panel of biomarkers useful for determining the stage of sepsis syndrome in the animal species, where the biomarkers are selected, for example, according to methods described herein. The amounts of the biomarkers can be measured in the biological sample--a score for the biological sample generated using a discrimination function determined for the stage of sepsis syndrome; and the score for the biological sample compared with a reference score. The reference score used for comparison may be, for example, a reference score determined using a biological sample from at least one animal at a given stage of sepsis syndrome. In some embodiments of these inventions, the immunocompromised animal is known or confirmed to be infected by a sepsis-causing pathogen.

The invention also provides for methods of selecting a candidate drug for treating sepsis syndrome comprising: selecting a model system of sepsis syndrome, the model system comprising immunocompromised individuals from an animal species and a pathogen species capable of causing sepsis in the animal species, wherein the survival rate of immunocompromised infected animals in the model system is within a desired range (for example, 30-70% may be used to establish differences between survived and doomed animals; when treating, the survival rate will preferably approach 100% in comparison with the mortality rate without treatment); infecting experimental immunocompromised and control animals of the animal species with the pathogen species; administering a test drug to the experimental animals; obtaining biological samples from the experimental and control animals at one or more selected times following infection; and measuring the amounts of a plurality of analytes in the biological samples. Further, scores can be determined for the experimental and control animals using the discrimination function for the animal species at the appropriate time point. The test compound is a candidate drug for treating sepsis

syndrome if it is found effective in the model. Effectiveness can be evaluated based upon a change in disease outcome, or a change in the amounts of a panel of biomarkers, or in the scores determined using the discrimination function. The difference in score between the biological sample from the test animal and the control animal can further be evaluated based on its statistical significance.

In one preferred embodiment of the invention, the test compound for treating sepsis is a compound suspected as having or determined as having (e.g., from high-throughput screening, a cell-based assay, or the like) VEGF-modulating activity, such as a vascular endothelial growth factor (VEGF) inhibitor, an anti-vascular endothelial growth factor (VEGF) antibody, or a peptide or small molecule VEGF agonist or antagonist. In another embodiment, the potential compound for treating sepsis is a compound suspected or determined as having activity in modulating a toll-like receptor (TLR), e.g., a TLR inhibitor. In yet another embodiment, the test compound is an anti-MCP-1 (or anti-JE) antibody. In yet another embodiment, the potential treatment comprises a PPARγ agonist, such as rosiglitazone. In a still further embodiment, the test compound is a reactive oxygen species or an antioxidant, such as ethyl pyruvate. In an additional embodiment, the test compound is a CCR2 modulator, more preferably a CCR2 inhibitor.

The invention also provides methods of determining a reference score for a group of immunocompromised infected animals in a model system, comprising: providing a model system of sepsis syndrome, the model system comprising immunocompromised survived animals and immunocompromised doomed animals from an animal species and a sepsis-causing pathogen species; infecting the animals in the model system; obtaining biological samples from the animals at one or more selected times after infecting; measuring the levels of a panel of biomarkers selected using the methods described herein in each biological sample; and determining a first reference score for immunocompromised survived animals using a discrimination function, and determining a second reference score for immunocompromised doomed animals using a discrimination function.

To further understand the invention, a glossary of various terms is provided below. The invention is also described in reference to various publications, the disclosures of which are incorporated by reference herein for the sake of brevity. Unless defined herein or indicated otherwise by context, the technical or scientific terms used herein have the same meaning as they would to one of ordinary skill in the art.

The terms "comprising", "including", and "containing" are used in their open, non-limiting sense.

An "analyte" is a specific substance of interest present in a biological sample and being analyzed, e.g., by the methods of the present invention. In the case of analytes related to infection and sepsis, these may include, for example, the inflammatory mediators that appear in circulation as a result of the presence of microorganisms and their components, including gram positive cell wall constituents and gram negative endotoxin, lipopolysaccharide, lipoteichoic acid. These inflammatory mediators include tumor necrosis factor (TNF), interleukin-1 (IL-1) and other interleukins and cytokines. Analytes may also refer to biochemicals, e.g., proteins, nucleotides, peptides, or siRNA's produced by cells in response to inflammatory mediators. Other analytes may include drugs of abuse, hormones, toxins, therapeutic drugs, markers of cardiac muscle damage.

An "animal" refers to a human or non-human mammal, including laboratory animals such as rodents (*e.g.*, mice, rats, hamsters, gerbils and guinea pigs); farm animals such as cattle, sheep, pigs, goats and horses; and domestic mammals such as dogs and cats, and ; birds, including domestic, wild and game birds such as chickens, turkeys and other gallinaceous birds, ducks, geese, and the like. The term does not denote a particular age. Thus, both adult and newborn or immature individuals are intended to be covered.

"Bacteremia" is the presence of bacteria in the blood.

A "biological sample" is an aliquot of body fluid or tissue withdrawn from an animal, for example, a human. In one embodiment, the biological fluid is whole blood. Examples of other biological samples include cell-containing compositions such as red blood cell concentrates, platelet concentrates, leukocyte concentrates, plasma, serum, urine, bone marrow aspirates, cerebrospinal fluid, tissue, cells, and other body fluids, including lymph aspirate, bronco-alveolar lavage, ascitis and essudates obtained from an infection site, as well as tissues, including homogenized organs.

A "biomarker" is any physiological substance measurable in a biological sample that is informative of the state of the animal from which the sample was taken, for example, the state of its immune system. A biomarker is considered to be informative if a measurable aspect of the marker is associated with the state of the animal. For a particular molecule identified as a marker, the measurable aspect of the marker that is associated with the state of the animal may include, for example, the concentration, amount, expression, or level of expression of the particular molecule.

A "candidate drug" or "test drug" refers to any compound or molecular entity or substance whose efficacy can be evaluated using the test animals and methods of the present invention. Such compounds or drugs include, e.g., chemical compounds, pharmaceuticals, antibodies, polypeptides, peptides, including soluble receptors, polynucleotides, and polynucleotide analogs, DNA, RNA, siRNA, or mixtures or chimeric molecules comprising one or more of these compounds or drugs. Many organizations (*e.g.*, the National Institutes of Health, pharmaceutical and chemical corporations) have large libraries of chemical or biological compounds from natural or synthetic processes, or fermentation broths or extracts. Such compounds can be employed in the practice of the present invention.

A "control animal" refers to an animal that has not been subject to a treatment (*e.g.*, exposure to a test drug) which might affect the progress of bacterial sepsis in the animal.

A "control sample" is a biological sample used for comparison with a test biological sample. A control sample may be taken from either a healthy mammal/individual or from a mammal/individual known to be infected with a sepsis-causing pathogen at any particular stage of interest.

A "control amount" of an analyte is the amount of an analyte determined to be present in a control sample.

A "diseased animal" refers to an animal afflicted with sepsis, severe sepsis, or septic shock.

A "discrimination function" is a linear function of measured variables. The discrimination function can be used to compute a score for each individual based on the measured variable. For example, a score below a given threshold can be used to classify an individual as belonging to one group, and a score above that threshold can be used to classify an individual as belonging to another group.

A "doomed" individual is defined as an animal with sepsis that is observed to die, or is predicted (or has a prognosis) to die, as a result of the disease based on exhibition of symptoms correlated with death due to sepsis. Similarly, a "doomed immunocompromised" individual is one observed to die from sepsis or reach a state of predicted nonrecovery from the disease.

"Immunocompromised" is used to describe an animal that has an impaired immune response to infection relative to another animal for any reason, including, e.g., exposure to irradiation, treatment with cytostatic drugs or other treatments, genetic alteration, age, or disease status.

"Linear discriminant analysis" (or LDA) is a technique for data classification in which a score is computed for each test subject. The score is a linear function of the measured variables. Scores below a threshold are predicted to belong to one group, and scores above the threshold are predicted to belong to another group.

"Multiple organ dysfunction syndrome" (or MODS) is the presence of altered organ function in an acutely ill patient such that homeostasis cannot be maintained without intervention.

A "principle component analysis" (or PCA) is a statistical technique for data dimensionality reduction.

A "reference score" is used to describe a score corresponding to a particular stage of sepsis obtained by applying a discrimination function to measurements of a panel of biomarkers tested in each of a group of animals in a model system for sepsis syndrome. The score can be used as a reference, or comparison point, to stage sepsis in test animals.

A "score" is a number obtained by applying a discrimination function to values obtained by measuring the concentrations of a panel of biomarkers in an animal. The score is indicative of the disease state of the animal.

A "selected timepoint" is a point in time at which a biological sample is taken from a subject for analysis, for example, measurement of a panel of biomarkers and subsequent score calculation.

"Sepsis," "severe sepsis," and "septic shock" are stages of sepsis as described by, e.g., American College of Chest Physicians and the Society of Critical Care Medicine Consensus Definitions, published in 1992. "Sepsis Syndrome" is interchangeable with the term "severe sepsis." The course by which a sepsis patient may progress either to death or hospital discharge is well known and has been described as a continuum from a state termed systemic inflammatory response syndrome (SIRS) to successive states of sepsis, severe sepsis, septic shock, multiple end-organ failure (MODS) and death (Rangel-Frausto, M S. JAMA 11:117-123 (1995)). In 1991 experts recruited by the American College of Chest Physicians and the Society of Critical Care Medicine met to reach a consensus on the diagnosis of sepsis and its sequelae. Their consensus definitions, published in 1992 (Bone RC et al., American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis, Chest 101:1644-1655) have provided a foundation for the common reporting and discussion of various interventions in patients with sepsis. According to the Consensus Definitions set

forth in Levy, et al., Crit. Care Med 2003;31:1250-6, Systemic Inflammatory Response Syndrome (SIRS) is defined as a systemic response to inflammatory processes, regardless of its etiology. SIRS is the presence of two or more of the following clinical signs: (i) body temperature > 38°C or < 36°C; (ii) heart rate greater than 90 beats per minute; (iii) respiratory rate > 20 breaths/minute and $PaCO_2$ < 32 mm Hg; (iv) white blood cell count >12,000/µl or < 4,000/µl or > 10% immature (band) forms. Sepsis is a clinical syndrome defined by the presence of both infection and a systemic inflammatory response. A list of possible signs of systemic inflammation in response to infection is listed in Table I of the Consensus report, "Diagnostic criteria for sepsis" as follows: infection, documented or suspected, and some of the following: general variables: fever (core temperature >38.3°C), hypothermia (core temperature <36°C), heart rate >90 min^{-1} or >2 SD above the normal value for age, tachypnea, altered mental status, significant edema or positive fluid balance (>20 mL/kg over 24 hrs), hyperglycemia (plasma glucose >120 mg/dL or 7.7 mmol/L) in the absence of diabetes; inflammatory variables: leukocytosis (WBC count >12,000 μL^{-1}), leukopenia (WBC count <4000 μL^{-1}), normal white blood count (WBC) with >10% immature forms, plasma C-reactive protein >2 SD above the normal value, plasma procalcitonin >2 SD above the normal value; Hemodynamic variables: arterial hypotension (SBP <90 mm Hg, MAP <70, or an SBP decrease >40 mm Hg in adults or <2 SD below normal for age), SvO_2>70%, cardiac index >3.5 $L{\bullet}min^{-1}{\bullet}M^{-23}$; organ dysfunction variables: arterial hypoxemia (PA_{O_2}/F_{IO_2} <300), acute oliguria (urine output <0.5$mL{\bullet}kg^{-1}{\bullet}hr^{-1}$ or 45 mmol/L for at least 2 hrs), creatinine increase >0.5 mg/dL, coagulation abnormalities (INR >1.5 or aPTT >60 secs), ileus (absent bowel sounds), thrombocytopenia (platelet count <100,000 μL^{-1}), hyperbilirubinemia (plasma total bilirubin >4 mg/dL or 70 mmol/L); tissue perfusion variables: hyperlactatemia (>1 mmol/L), decreased capillary refill or mottling. In the report, the authors point out that frequently, infection is strongly suspected without being microbiologically confirmed, and therefore sepsis (infection and the systemic response to it) may only be strongly suspected, without being microbiologically confirmed. Severe sepsis is sepsis complicated by organ dysfunction, hypotension, or hypoperfusion. Hypoperfusion and perfusion abnormalities may include lactic acidosis, oliguria, or an acute alteration in mental status. Organ dysfunction can be defined using the definitions developed by Marshall et al. (Crit Care Med 1995; 23:1638-1652) or the definitions used for the Sequential Organ Failure Assessment (SOFA) score (Ferreira, *et al.*, JAMA 2002; 286:1754-1758). Organ dysfunction in severe sepsis in

the pediatric population has been defined by Wilkinson *et al.*, Crit Care Med 1986; 14:271-274, Proulx *et al.*, Chest 1996; 109:1033-1037, and Doughty *et al.* (Crit Care Med 1996; 109:1033-1037) or using definitions for the PEMOD and PELOD score (Leteutre, *et al.*, Med Decis Making 1997). Septic shock refers to a state of acute circulatory failure characterized by persistent arterial hypotension unexplained by other causes. Septic shock in pediatric patients is a tachycardia (may be absent in the hypothermic patient) with signs of decreased perfusion, including decreased peripheral pulses compared with central pulses, altered alertness, flash capillary refill or capillary refill > 2 secs, mottled or cool extremities, or a decreased urine output. Hyoptension is a sign of late and decompensated shock in children.

"Significance level" is the probability of a false rejection of the null hypothesis in a statistical test.

"Staging" means determining a reference point reflecting disease status, progression, or disease outcome by measuring concentrations of disease biomarkers.

A "subject" is an individual on which experimentation is performed, such as a human or another animal, healthy or diseased.

"Survived" as used herein refers to an individual with sepsis that is observed to survive after a determined period of time following infection or to recover from infection. Similarly, a "survived immunocompromised" individual is an immunocompromised individual observed to survive or recover from sepsis.

A "test animal" is an animal with sepsis, sepsis syndrome or septic shock that is under evaluation using the methods of the invention.

A "T-test" is a statistical test done to assess whether the difference between the means of two groups is statistically significant.

One general aspect of the invention relates to an immunocompromised mouse model. The invention contemplates the use of any animal susceptible to sepsis syndrome in the model system. Establishing immunosuppression can be accomplished by various means, including, e.g., sublethal irradiation using a gamma irradiator with varying doses, *e.g.*, 50 – 600 rads or even greater. Irradiation of animals to produce an immunosuppressed state has been described extensively in the art. Immunosuppression can also be achieved by treatment of the animal with cytostatic drugs, including antibodies against T-cell targets, and drugs used to ablate the bone marrow, as well as through the use of animals with defective immune systems due to genetic causes. In general, any treatment or condition that increases the relative susceptibility of a subject to infections is contemplated. For example, individuals

that are very young, very old, or debilitated by another disease are immunocompromised or immunoincompetent and, compared to a healthy individual, those individuals are more susceptible to infection. Further, the model can include animals that are not known to be immunecompromised but are being tested for increased susceptibility to infection due, for example, to genetic defects that predispose them to infection and bacteremia. With regard to the study of human subjects, this invention contemplates testing samples taken from humans who have been rendered immunosuppressed by their disease condition, or by drug treatment administered to treat a disease such as cancer.

The animals of the model can be infected by various methods known and used in the art, including, e.g., use of the murine pouch bacterial load assay (Fuursted, *et al.*, "Significance of Low-Level Resistance to Ciprofloxacin in *Klebsiella Pneumoniae* and the Effect of Increased Dosage of Ciprofloxacin *In vivo* Using the Rat Granuloma Pouch Model," Journal of Antimicrobial Chemotherapy 50: 421-424, 2002) and with any of a multitude of pathogen species, including, *e.g.*, a bacterium species selected from the group consisting of Enterococcus spp., Staphylococcus spp., Streptococcus spp., Enterobacteriacae family, Providencia spp., Pseudomonas spp. and others, including Gram negative, Gram positive bacteria, fungi and viruses. Various potential vehicles for inoculation, including mucin or phosphate-buffered saline, are known in the art and may be used as suitable. It is also known in the art that concentrations of bacteria in the inoculum can vary, *e.g.* 100,000 to 100,000,000 organisms depending on the experimental conditions. LPS or staphylococcal enterotoxin B (SEB) can be injected as a control. Zymosan, for example at a dose of 2.5 mg, can be injected to potentiate bacterial invasion.

It is understood that in practicing the methods according to the present invention, the animals can be monitored as needed, *e.g.*, daily, until sepsis is established as determined by bacterial counts in the blood, white blood cell (wbc) counts, and blood levels of analytes associated with early stages of sepsis such as Tissue Necrosis Factor α, IL-1, IL-6, C reactive protein (CRP), as well as blood oxygen levels. All of these parameters are established as early markers of sepsis in humans. Fibrinogen and fibrinogen degradation products (FDP) are early indicators of Disseminated Intravascular Coagulation (DIC) and early indicators of severe sepsis. Further, the animals of the model can be treated with antibiotics following infection, in order to control bacteremia.

The number of animals included in a study can vary from one to many, as dictated by circumstances and the nature of the questions asked. Physical evaluation of the animals can

include observation for diarrhea, lethargy, ruffled fur, lack of appetite and poor body condition. Survival can be evaluated based on a physical evaluation of the animal after a prescribed amount of time, *e.g.*, an animal that remains healthy for one week (or another suitable interval) after the last animal in the study died or was euthanized can be considered survived. Analyte levels and other physiological parameters, including, e.g., blood cell counts, body temperature, and blood pressure, can also be measured to provide information regarding the health status of the animal. In general, the time elapsed between infection and progression of the doomed animals to the moribund state should allow for progression time and/or time to observe different stages of sepsis. The time interval should also allow for measuring differences between groups.

Using the animal model, potential treatments and targets for the systemic inflammatory response to infection can be evaluated. Potential treatments can be evaluated based upon their ability to increase survival rates. For example, the survival rate in immunocompromised, infected animals treated with an experimental drug can be compared with the survival rate in immunocompromised, infected animals not treated with the drug. A statistically significant increase in survival of the treated animals would be one indication that the treatment was effective for sepsis. A substantial increase, e.g. five, six, seven, eight, nine, ten, fifteen, twenty, twenty-five fold or more increase consistently observed from experiment to experiment, could also indicate effectiveness of a treatment. Potential targets can similarly be evaluated based on, for example, a change in survival rate when a model animal having a defective target pathway is used.

One use of the inventive modeling system is to identify panels of sepsis biomarkers that are predictive of disease outcome, including progression to septic shock vs. recovery, and survival vs. death. The panel of biomarkers can be selected by measuring the amounts of a larger number of analytes potentially associated with disease, and narrowing the number using the methods of the invention. The analytes can include any biological molecule suspected of being involved in sepsis, including markers of inflammation and molecules involved in the immune response, including cytokines; chemokines; coagulation factors, biomolecules known to be produced by cells in response to inflammation mediators, and others.

Biological samples can be taken from subjects at any time following infection, depending on the stage of disease under investigation. It is contemplated that timepoints can be taken periodically to follow the scores determined using one biomarker panel over the

course of disease through a selected outcome. It is further contemplated that more than one biomarker panel could be identified and followed over the course of disease, as certain biomarker panels might be more predictive of certain outcomes. A panel predictive of one outcome, *e.g.*, survival, might not be the best panel for predicting another outcome, *e.g.*, progression to septic shock.

Determination of sample size depends on the individual situation. Methods for determining appropriate sample sizes are known in the art. In general, sample size can be selected depending on the variation of the data (e.g., how closely the data are clustered), the power required to detect the difference, the difference between the means of the two groups being compared, and significance level used.

Elsewhere in this specification, numerous molecular analytes that can be used in determining a biomarker panel according to the present invention are listed. Testing of these and other analytes in plasma may be performed on a commercial basis from Rules-Based Medicine, Inc. (Austin, TX). Concentrations of the analytes can also be measured by methods known in the art. Large numbers of analytes can be measured rapidly using a microchip containing an analyte panel. There is ample literature describing molecular pathways involved in sepsis, which provide guidance for the selection of additional analytes to test. In addition, new analytes may be identified through proteomic and genomic studies by using those techniques to compare proteins expressed or genes transcribed in individuals with sepsis and individuals that do not develop sepsis during a bacterial infection.

Selection of a biomarker panel can be accomplished by performing a statistical analysis of the analyte measurement data, to determine which analytes measured were present at significantly higher levels in the doomed animals than in the survived animals. A statistically significant increase in survival of the treated animals would be one indication that an analyte could serve as a biomarker useful for studying sepsis. Empirical observation could also indicate the usefulness of a given analyte as a biomarker for sepsis. For example, a substantial change in the level of the analyte, *e.g.*, a change of five, six, seven, eight, nine, ten, fifteen, twenty, twenty-five fold or more, consistently observed from experiment to experiment, could indicate its use as a biomarker. Other factors observed by the researcher, *e.g.*, the time course of increasing and decreasing concentrations of analytes, could also influence the decision to include an analyte in the biomarker panel.

Based on the statistical significance of the difference in analyte concentration between doomed and survived animals, a biomarker panel can be selected. For example, the data can

be transformed to the log scale (natural base), and T-tests can be performed on the dataset for each analyte. Alternatively the data can be analyzed by other univariate statistical analyses, including using nonparametric Wilcoxon two-sample test for each analyte. Analytes are selected for use as biomarkers at the significance level of 0.05 or better.

A discrimination function using the analytes in the selected biomarker panel can be derived and used to calculate a score for each animal tested. The score is used to discriminate among animals with different disease outcomes, for example, animals that survive vs. animals that die. A discrimination function can be derived by first performing a principle component analysis on the biomarkers. This analysis reveals how much each of the principle components contributes to explaining the variation in the original data. Principle components can be selected to explain at least (95%) of the original data, potentially resulting in a reduction of the dimensionality of the data. Selecting a higher percentage, or a greater number of principle components, results in less information lost, but also less reduction in dimensionality. Determining the minimum percentage can therefore depend on how much information a researcher wishes to retain, and what level of reduction of the dimensionality of the dataset is desired.

In deriving the discrimination function, a linear discriminant analysis is performed on remaining principle components. This is done to provide the best linear combination of the principle components, in terms of maximizing the difference in scores observed between doomed and survived animals.

The number of biomarkers selected for a given panel can vary as preferred by the researcher. In one embodiment of this invention, the panel consists of fifteen or fewer biomarkers; however, use of more than fifteen biomarkers is contemplated depending on the results of the analyte measurements and the needs and preferences of the researcher. In another embodiment of the invention, the panel consists of ten or fewer biomarkers, and in other embodiments, the panel consists of five biomarkers or even as few as one biomarker.

The ability of the biomarkers to predict disease outcome can be evaluated using a visualization-based analytical tool, *e.g.*, OmniViz Analysis® software, to observe patterns in data generated using the biomarker panel. The patterns may be visualized using a plot or galaxy map, in which the level of similarity of the data is represented by the proximity of the datapoints on the map. Patterns which indicate similarity in plot location among biomarker data derived from biological samples taken from animals in the same outcome group indicate that the biomarker panel used is predictive of disease outcome.

In another general aspect of the invention, a method is provided by which an identified biomarker panel is used to predict disease outcome in a test animal. The biomarker panel is measured in a biological sample taken from a test animal, and a score is calculated based on the discrimination function previously derived using the same biomarker panel. The scores may be plotted as described in the examples below, and a threshold value selected to maximize accuracy in predicting one outcome. For example, the threshold value can be set to predict death with 100% accuracy. As described in the examples, when such a threshold was set, this method was found to predict survival with 62.5 – 100% accuracy. The biomarker levels can also be evaluated empirically, based on substantial differences observed consistently from experiment to experiment.

Disease outcome can also be predicted using the methods of the invention through the use of information obtained by comparing in groups of animals observed to have different disease outcomes factors such as survival vs. death or the ratio of the level of each biomarker found in animals with one outcome to the level in animals with the other outcome. A consistently high or low ratio can be considered indicative of the outcome observed, and therefore a similar ratio observed in a test animal can be used to indicate the outcome in the test animal. Similarly, ratios observed in the model can be applied to the testing of treatments for sepsis. Treated animals that experience a positive outcome, *e.g.*, survival, despite having biomarker ratios indicative of the corresponding negative outcome, *e.g.*, death, prior to or around the time of treatment can be considered to have been treated with a drug candidate warranting further development. Distinctive biomarker ratios can also be indicative of infection stage, if consistently observed at a given timepoint following infection. These ratios, in combination with other information, for example, patient history, can be applied to the staging of sepsis in animals at unknown stages of infection. Diagnostic criteria including those proposed in Crit Care Med 2003, 4:1250-1256 2001, SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference can be combined with results obtained using methods according to the invention to help evaluate the staging of sepsis or monitor a patient. For example, biomarker levels or scores could be correlated with a patient's genotype information, as some individuals are likely genetically predisposed to be more or less sensitive to the effects of particular cytokines.

Potential outcomes predicted can include death, progression to various stages of sepsis, including sepsis syndrome and septic shock, and changes in physiological parameters, including white blood cell count, red blood cell count, platelet count, body temperature, body

weight, and blood pressure. Other disease outcomes can include the observance of a particular level of an analyte, or death due to different causes. Still other outcomes are contemplated, including response to a drug or treatment, for example, failure to respond to a drug or treatment as expected.

In another general aspect, the invention is directed to methods for staging sepsis syndrome and evaluating potential treatments. Progression of sepsis and sepsis syndrome can be affected by many factors, including pathogen species, inoculum, mode of entry, preexisting disease, the health, age and genetic background of the individual, quality of care, and drugs being taken for other indications. The animal model of the invention can be used to evaluate the ability of potential sepsis treatments to influence disease outcome. Immunocompromised, infected animals treated with a potential sepsis drug or compound can be compared with control animals not given the treatment. The ability of the treatment to alter disease outcome is evaluated by comparing outcome in the two groups. For example, a statistically significant increase in survival rate of the treated animals relative to the control animals would indicate effectiveness of the treatment in preventing death.

Biomarker panels identified according to the invention can also be used in the evaluation of treatments for sepsis, sepsis syndrome and septic shock. A panel of biomarkers, and similar panels identified using the methods of the invention, can be used to predict disease outcome in individuals to be treated with a potential sepsis drug, compound or other treatment. The predicted outcome can then be compared with the outcome observed following administration of the treatment. The efficacy of the treatment can thus be evaluated by a change in the observed outcome of the individuals receiving the treatment in comparison to the outcome predicted for those individuals either prior to treatment or shortly thereafter.

A number of receptors, proteins, and the like implicated in mediating sepsis or sepsis syndrome have been considered and described in the literature (Cohen, J., "The Immunopathogenesis of Sepsis," Nature 420:885-891, 2002; Netea, *et al.*, "Proinflammatory Cytokines and Sepsis Syndrome: not enough, or too much of a good thing?" Trends in Immunology 24[5]:254-258, 2003). These as well as others that are described herein represent sepsis drug targets--i.e., biological targets that, through modulation of their activity with a drug, may be upregulated, downregulated, inhibited, agonized, antagonized, or the like for therapeutic treatment of the disease or symptoms or medical conditions associated with it.

For example, vascular endothelial growth factor (VEGF), which is expressed in a variety of cell types, including macrophages, is such a target. In macrophages, VEGF has been shown to be upregulated by the inflammatory mediator lipolpoysaccharide (LPS) and by engagement of CD40 by CD40 ligand (CD40L). LPS and CD40L activate nuclear factor κB (NF-κB) in monocytes. VEGF production in human macrophages has been shown to be NF-κB-dependent. NF-κB regulates many of the genes involved in immune and inflammatory responses (Kiriakidis *et al.*, Journal of Cell Science 116:665-74, 2003). Increased levels of VEGF may be found in doomed immunocompromised animals using methods according to the invention.

Monocytes have been considered the most important cells in orchestrating the innate immune response against bacteria. Recent studies have shown that mast cell deficient mice are less efficient in surviving experimentally induced infections, indicating that mast cells also play a fundamental role in the defense against bacterial infection.

Mast cells originate from hematopoietic bone marrow precursors, circulate in the peripheral blood as immature progenitors, and complete their differentiation in the mucosal and connective tissues in a microenvironment-characteristic manner. *In vitro* studies have shown that mast cells, upon contact with bacteria, release a variety of mediators, initiating a cascade of events leading to increased capillary permeability and the egress of antibodies, complement, and inflammatory cells into tissues. This event is likely initiated by the direct interaction of microbial components with pattern recognition receptors, such as toll-like receptors (TLRs) 2, 4, 6 and 8, and the FimH receptor CD48 for E. coli fimbriae.

Importantly, mast cells are the only cells that store preformed pro-inflammatory factors, *e.g.*, tumor necrosis factor α (TNF-α) and IL-8. Since mast cells are distributed along the interface with the external environment at the portals of entry of many infectious agents, and given the immune functions associated with mast cells, we believe that mast cells are key players in preventing systemic spread of bacteria and possibly also in the development of septic shock. Therefore, compounds affecting the activity of the TLRs should be useful in treating sepsis syndrome. Furthermore, involvement of mutations in a TLR, TLR4, has been implicated in death by septic shock.

Other test compounds contemplated by the invention are those that increase vascular permeability, as death due to septic shock may be attributed to hypotension and poor tissue

perfusion and oxygenation. Compounds that influence or increase oxygen delivery to the tissues are also contemplated for testing or sepsis modeling.

Numerous compounds are described in the literature as having activity against one or more of the biomarkers described herein, and therefore may be evaluated in a sepsis model according to the invention. Examples of such compounds against various targets include, e.g.: Published Patent Application No. US 2004/0209929 (PPAR agonists); Published Patent Application No. US 2004/0186166 (Peroxisome Proliferator Activated Nuclear Receptor Gamma (PPARγ) activators); Published Patent Application No. US 2004/0162354 (PPARγ agonists); U.S. Patent No. 6,670,364 (MCP-1 antagonists); Published Patent Application No. US 2004/0186143 (modulators of chemokine receptor or MCP-1 activity); Published Patent Application No. US 2004/0198719 (MCP-1 antagonists); Published Patent Application No. US 2004/0151721 (CCR2 antibodies, etc.); Published Patent Application No. US 2004/0186140 (modulators of MCP-1 function); Published Patent Application No. US 2004/0198719 (MCP-1 antagonists); and Published Patent Application No. US 2004/0171551 (MCP-1 ligands). Additionally, antibodies against such targets may also be tested, such as anti-VEGF antibodies or anti-MCP-1 antibodies (see, e.g., U.S. Provisional Application No. 60/584,365, the disclosure of which is incorporated by reference herein).

The discovery of biomarkers could identify new drug targets for sepsis. One such target discovered using methodology in accordance with the invention is MCP-1. Thus, another general aspect of the invention relates to methods of treating sepsis comprising administering to a subject in need of such treatment an effective amount of compound that modulates MCP-1 activity. Illustrative compounds useful for treating sepsis include those exemplified above.

The term "treating" includes reversing, alleviating, lessening, or inhibiting the progress of sepsis or a stage thereof, or one or more symptoms of such disorder or condition. In therapeutic applications, a composition containing an MCP-1-modulating compound may be administered to a patient already suffering from sepsis in an amount sufficient for treatment, i.e., a therapeutically effective amount or dose. The selection of an amount effective for this use will depend on the severity and course of the proliferative disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. The amount and frequency of administration of the compounds used in the methods described herein and, if applicable, other agents will be selected within suitable ranges, which may be determined by standard techniques such as

dose-escalation studies, according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the patient as well as severity of the disease. However, an illustrative effective dosage is in the range of about 0.001 to about 100 mg per kg body weight per day, or from about 1 to about 35 mg/kg/day, in single or divided doses. For a 70 kg human, this would amount to from about 0.05 to about 7 g/day, of from about 0.2 to about 2.5 g/day. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effect, provided that such larger doses are first divided into several small doses for administration throughout the day.

The present invention contemplates the identification or evaluation of compounds for their efficacy in treating sepsis. To be an effective treatment, the administration of which results in a statistically significant change in the levels of one or more panel biomarkers measured at a given time following infection. A change in disease outcome might not be observed if only one or two of the biomarkers were affected; however, the invention also contemplates combining two or more treatments identified in this manner to influence disease outcome.

Other sepsis targets include chemokines, *e.g.* CXCL5/GCP-2 (chemokine [C-X-C motif] ligand 5; granulocyte chemotactic protein-2), CXCL10/IP-10 (CXCL10: chemokine [C-X-C motif] ligand 10; interferon-inducible cytokine IP-10), IL-8/KC/GROα (interleukin 8), MCP-1/CCL2 (chemokine [C-C motif] ligand 2; monocyte chemoattractant protein-1), MCP-3/CCL7 (chemokine [C-C motif] ligand 7; monocyte chemoattractant protein 3), MCP-5/CCL12 (chemokine [C-C motif] ligand 12), MIG/CXCL9 (chemokine [C-X-C motif] ligand 9; monokine induced by gamma interferon), MIP-1α/CCL3 (chemokine [C-C motif] ligand 3; macrophage inflammatory protein-1 alpha), MIP-1β/CCL4 (chemokine [C-C motif] ligand 4; macrophage inflammatory protein-1 beta), MIP-2/CXCL2 (chemokine [C-X-C motif] ligand 2), RANTES/CCL5 (chemokine [C-C motif] ligand 5); coagulation factors, *e.g.*, Bdk (bradykinin), PAF (platelet activating factor), TF (tissue factor), TFPI (tissue factor pathway inhibitor), and vWF (von Willebrand factor); cytokines, *e.g.*, GM-CSF/CSF2 (colony stimulating factor 2 [granulocyte-macrophage]), HMGB1 (high-mobility group box 1), IFNγ (interferon gamma), IL-10 (interleukin 10), IL-11 (interleukin 11), IL-12p70 (interleukin 12; p70 subunit), IL-17 (interleukin 17), IL-18 (interleukin 18 [interferon-

gamma-inducing factor]), IL-1α (interleukin 1a), IL-3 (interleukin 3), IL-6 (interleukin 6), IL-7 (interleukin 7), LIF (leukemia inhibitory factor [cholinergic differentiation factor]), MIF (macrophage migration inhibitory factor), OSM (oncostatin M), and TNFα (tumor necrosis factor alpha); molecules involved in innate immunity, *e.g.*, C5a (complement component 5), CRP (C reactive protein), iNOS (inducible nitric oxide synthase), MBL (mannose binding lectin), TREM1(triggering receptor expressed on myeloid cells 1), and other molecules, including, SCF/KITLG (stem cell factor; KIT ligand), EDN1(endothelin 1), PLA2 (phospholipase A2), HIF1A (Hypoxia inducible factor 1), TIMP-1 (tissue inhibitor of metalloproteinase 1 [erythroid potentiating activity, collagenase inhibitor]). The present invention is useful for evaluating test compounds or drugs for use in various stages of sepsis, e.g., sepsis syndrome and septic shock.

Reference scores determined using a biomarker panel identified using the methods of the invention can also be useful for staging disease, and can therefore be used to predict disease outcome and evaluate the effectiveness of a potential sepsis treatment. A reference score can be determined by general techniques known in the art based on scores calculated for individuals in a group of animals. The reference scores can be used to evaluate scores calculated using samples taken from test animals. For example, based on known reference scores for a particular disease outcome, an animal found to have a score indicative of that outcome can be predicted to experience that outcome. Reference scores can also be used to decide when a treatment should be administered to an animal. For example, a treatment determined to be effective when administered to animals having a certain reference score can be given to a test animal when its score is found to be within a reasonable range of the reference score.

Various exemplary embodiments of the invention are described below.

EXAMPLES

Example 1 – Infectious Immunocompromised Mouse Model

Initially, C3H/HeJ mice were compared with C3H/HeN normal mice in a pouch model for their ability to survive infection. Mice of strain C3H/HeJ are defective in the TLR4 receptor and do not undergo LPS-induced shock. The mice were anesthetized with isofluorane, shaved in the area caudal to the ears, and a pouch was created by subcutaneous injection of 2-3 ml of air followed by the subcutaneous injection of 0.2 ml of a 0.5% solution of croton oil in olive oil. Either four days (d4) or five days (d5) later, animals were checked for the presence of a pouch. The number of animals observed to have pouches at these times

are shown in Table 1 below, under the columns "d4" and "d5." Animals without pouches were discarded. E.coli bort was injected in the pouches as reported in the first column of Table 1.

All animals of the HeJ strain were euthanized due to terminal health conditions, starting at 18.5h and lasting until 48h post-injection. All the HeN mice survived.

Table 1

Bacteria Strain	Mouse Strain	d4 pouches	Bacterial Dose	Euthanized	d5 Pouches	Bacteria Dose	Euthanized
E. coli Bort	HeJ	2	$1.2x10^7$	22h, 40.5	2	$1.2x10^7$	18.5h, 18.5h
		3	$1.2x10^6$	22h, 29h	2	$1.2x10^6$	29h, 29h
		3	$1.2x10^5$	22.5h, 24h, 29.5	1	$1.2x10^5$	40.5h
	HeN	2	$1.2x10^7$	survived	2	$1.2x10^7$	survived
		3	$1.2x10^6$	survived	2	$1.2x10^6$	survived
		3	$1.2x10^5$	survived	2	$1.2x10^5$	survived

Next, survival of sublethally irradiated C3H/HeN was compared with that of C3H/HeJ. Five days after being injected with oil, 11 of the 22 HeN animals were given a 350 rad dose of irradiation. The same day, E.coli bort was injected in the pouches (7 of 14 HeJ; 6/11 irradiated HeN and 6/11 HeN) at the dose of 1x106. The following day, 20 to 24h after bacterial injection, blood samples were taken to test for the presence of bacteria. There was no bacterial growth from the blood of non irradiated HeN. 5/7 HeJ and 2/6 XR (irradiated) HeN were bacteremic. All HeJ animals became terminally ill and had to be euthanized, and only one of the irradiated HeN animals was euthanized.

Table 2

Bacteria Strain	Mouse Strain	d5 Pouches	Bacteria Dose	Euthanized	Bacterial Growth at 20-24h
E.coli Bort	HeJ	7	NONE	NONE	ND
		7	$1x10^6$	ALL	5/7 pos
	HeN	5	NONE	NONE	ND

	6	$1x10^6$	NONE	no growth
HeN XR				
350 rads	5	NONE	NONE	ND
	6	$1x10^6$	1/6	2/6 pos

As apparent from the data shown above, otherwise healthy animals from the C3H/HeN strain do not succumb to infection in the pouches with infection of up to 1.2×10^7 bacteria. Animals that have a mutation in the TLR 4 receptor, C3H/HeJ, and therefore cannot interact with E. coli LPS, develop bacteremia and a final disease state requiring euthanasia with as few as 1.2×10^5 bacteria. One out of six animals of the HeN strain that received an irradiation dose equivalent to 350 rads became susceptible to infection and required euthanasia.

In the next experiment, 37 C3H/HeN mice were pouched according to the procedure described above. One day later, 17 mice received 420 rads irradiation from a gamma irradiator. Five days after irradiation, $1.5x10^6$ bacteria (E. coli bort) in 0.1 ml PBS were injected into the subcutaneous pouches of 7 irradiated mice and 7 non-irradiated mice. The remaining mice were not injected with bacteria (see Table 3). After infection, animals were checked daily for signs of pain and distress, including diarrhea, lethargy, ruffled fur, lack of appetite and poor body condition. Animals were euthanized when very lethargic as defined as being unresponsive (lacking movement) when touched. Under these conditions the animals die within 6-12 hours. At 22 hours after infection, blood samples for analysis were taken from all 37 mice. By 6 days after infection, 3 of the irradiated, infected mice had to be euthanized based on clinical criteria for euthanization, and were euthanized using CO_2. All the other animals survived.

Table 3

	Pouch	XR 420rads	E.coli Bort $1.5x10^6$	RBM	Comments	Tag No.	Time of blood collection	CFU/25ulblood	WBC	PLT
Group 1	no	no	no			2254	22 hours	0	4.7	926
	no	no	no	yes		2255	22 hours	0	5.8	1060
	no	no	no			2256	22 hours	0	5.7	957
	no	no	no	yes		2257	22 hours	0	6.0	1010
	no	no	no			2258	22 hours	0	4.8	897

					Average				**5.4**	**970**
Group 2	yes	no	no			2264	22 hours	0	6.4	988
	yes	no	no			2265	22 hours	0	6.6	954
	yes	no	no	yes		2266	22 hours	0	6.9	1068
	yes	no	no			2267	22 hours	0	7.0	963
	yes	no	no	yes		2268	22 hours	0	5.6	1072
	yes	no	no			2274	22 hours	0	6.7	898
	yes	no	no			2275	22 hours	0	5.0	998
	yes	no	no			2276	22 hours	0	5.9	986
					Average				**6.3**	**991**
Group 3	yes	no	yes	yes		2277	22 hours	4	4.3	323
	yes	no	yes	yes		2278	22 hours	1	4.0	396
	yes	no	yes	yes		2279	22 hours	0	4.9	467
	yes	no	yes	yes		2280	22 hours	0	4.9	526
	yes	no	yes	yes		2281	22 hours	0	5.2	561
	yes	no	yes	yes		2282	22 hours	0	5.2	698
	yes	no	yes	yes		2283	22 hours	0	6.0	732
					Average				**4.9**	**529**
Group 4	no	yes	no	yes		2259	22 hours	0	2.5	629
	no	yes	no			2260	22 hours	0	2.8	481
	no	yes	no			2261	22 hours	0	2.0	478
	no	yes	no			2262	22 hours	0	2.1	465
	no	yes	no	yes		2263	22 hours	0	1.8	627
					Average				**2.2**	**536**
Group 5	yes	yes	no			2269	22 hours	0	2.2	475
	yes	yes	no			2270	22 hours	0	2.2	288
	yes	yes	no	yes		2271	22 hours	0	1.6	502
	yes	yes	no	yes		2272	22 hours	0	2.6	567
	yes	yes	no			2273	22 hours	0	2.7	273
					Average				**2.3**	**421**
Group 6	yes	yes	yes	yes		2284	22 hours	19	2.0	102
	yes	yes	yes	yes		2285	22 hours	21	2.0	149
	yes	yes	yes	yes		2286	22 hours	100	2.7	197
	yes	yes	yes	yes	Euthanized at 48h	2287	22 hours	113	1.4	97
	yes	yes	yes	yes	Found dead at 28h	2288	22 hours	400	1.7	85
	yes	yes	yes	yes		2289	22 hours	0	3.4	139

yes	yes	yes	yes	Euthanized at 144h	2290	22 hours	79	1.7	133
				Average				2.1	128.9
yes	yes	yes	yes		2287	Final	n/c	3.0	111
yes	yes	yes	yes		2290	Final		5.3	46

Blood samples were analyzed for bacterial counts, white blood cells (WBC), and platelets (PLT). Plasma was obtained from the blood samples and some samples were sent to Rules-Based Medicine, Inc. (RBM) for analyte measurement. Samples sent to RBM for analysis were: 2255, 2257, 2266, 2268, 2277, 2278, 2279, 2280, 2281, 2282, 2283, 2259, 2263, 2271, 2272, 2284, 2285, 2286, 2287, 2288, 2289, 2290, 2287 Final, and 2290 Final. The data obtained by RBM are shown in the table at Appendix A (Experiment c). In the table at Appendix A, which has columns A-Z, AA-AZ, and BA-BK and rows 1-188, the column letter is printed across the top of each page and the row number is printed on the left hand side of each page.

Other experiments were performed similarly. In one experiment, all the animals used were irradiated. In that experiment, pouches were created in C3H/HeN according to the same procedures as described above. One day later animals received 413 rads. Six days after the pouches were created, pouches were infected by injecting 1.7×10^6 of E.coli bort in PBS. Twenty-two hours after infection, the animals were bled. Blood samples were analyzed for bacterial counts, WBC, and platelets. Plasma was obtained from the blood samples and some samples were sent to Rules Based Medicine for analyte measurement. Samples were sent to RBM at 3 different time points: March, June and September as indicated in Tables 4 and 5. The data obtained by RBM are shown in Appendix A (Experiment d).

Table 4

BLOOD SAMPLES COLECTED AT 22H AFTER INFECTION

Sample sent to RBM	Animal number	CFU/25ul blood	WBC	PLT
June	6505	2	3.3	442
June	6506	0	2.4	173
March	6507	0	2.8	200
March	6508	0	2.5	255

Table 5

BLOOD SAMPLES COLECTED AT EUTHANASIA

Sample sent to RBM	Health status at euthanasia	Animal number	Time of blood collection h	CFU/25ul blood
Sep	Healthy	6505	144	0
Sep	Healthy	6506	144	0
	Moribund	6507	288	ND
	Healthy	6508	ND	ND

June	6509	72	2.1	331
	6510	0	3	124
	6511	0	2.7	266
March	6512	0	3.3	230
	6513	0	2	154
March	6514	34	2.4	165
June	6515	5	2.5	141
June	6516	2	2.1	326
	6517	0	2.9	298
	6518	0	1.6	244
June	6519	0	2.9	303
June	6520	0	1.6	299
	6521	3	2.2	303
	6522	0	3.8	226
	6523	0	2.2	187
	6524	0	1.8	137
	6525	0	3.2	448
March	6526	1	1.6	221
	6527	0	2.7	313
June	6528	0	2.5	192
	6529	0	3.7	161
March	6530	250	2.5	226
	6531	10	2.3	261
March	6532	2	5.6	494
	6533	2	3.1	135
March	6534	0	1.8	127
March	6535	105	1.5	138
	6536	1	1.6	222
March	6537	0	3.7	450

June	Moribund	6509	115	TNTC
	Moribund	6510	67	ND
	Moribund	6511	170	ND
	Healthy	6512	ND	ND
	Moribund	6513	170	TNTC
	Moribund	6514	67	ND
March	Moribund	6515	75	TNTC
Sep	Healthy	6516	144	0
	Moribund	6517	92	ND
	Moribund	6518	75	TNTC
Sep	Healthy	6519	144	4
	Healthy	6520	92	ND
March	Moribund	6521	92	TNTC
	Moribund	6522	115	TNTC
	Moribund	6523	115	TNTC
	Moribund	6524	92	ND
	Moribund	6525	170	TNTC
	Moribund	6526	46	TNTC
	Moribund	6527	118	TNTC
June	Moribund	6528	92	TNTC
Sep	Healthy	6529	144	2
March	Moribund	6530	27	TNTC
March	Moribund	6531	92	TNTC
	Healthy	6532	ND	ND
	Moribund	6533	187	ND
June	Moribund	6534	50	TNTC
June	Moribund	6535	46	TNTC
	Moribund	6536	67	ND
	Healthy	6537	ND	ND

Another experiment (see Table 6) was performed using 25 C3H/HeN animals. In this experiment, pouches were created according to the same procedures as described above. One day later 20 animals received about 385 rads gamma irradiation. Six days after the pouches were created, pouches were infected by injecting 1.8×10^6 CFU of E.coli bort in PBS. Twenty-three hours after infection, the animals were bled and blood samples were analyzed for bacterial counts. Plasma was obtained from the blood samples and some samples were sent to Rules-Based Medicine for analysis. At the time of euthanasia, samples from

moribund animals were collected and 2 pools were prepared. Pool 1 contained terminal (final) samples from animals 6615, 6622, 6624, 6626, and 6630. Pool 2 contained terminal samples from animals 6627, 6628, and 6631. Aliquots from each pool were submitted to RBM for analysis. The data obtained by RBM are shown in Appendix A (Experiment e).

Table 6

Sample sent to RBM	XR 385rads	Animal number	CFU/25ul blood at 23hrs	CFU/25ul blood at Euthanasia	Time at Euthanasia h	Health status at Euthanasia
	Non-XR Infected	6609	0			Healthy
	Non-XR Infected	6610	42			Healthy
	Non-XR Infected	6611	1			Healthy
	Non-XR Infected	6612	0			Healthy
	Non-XR Infected	6613	0			Healthy
yes	XR Infected	6614	0			Healthy
yes	XR Infected	6615	1	TNTC	90	Moribund
yes	XR Infected	6616	0	TNTC	160	Moribund
	XR Infected	6617	0			Healthy
yes	XR Infected	6618	2			Healthy
	XR Infected	6619	0			Healthy
	XR Infected	6620	0			Healthy
	XR Infected	6621	0			Healthy
yes	XR Infected	6622	0	TNTC	96	Moribund
	XR Infected	6623	0		96	Moribund
	XR Infected	6624	0	TNTC	90	Moribund
yes	XR Infected	6625	0			Healthy
	XR Infected	6626	0	TNTC	96	Moribund
yes	XR Infected	6627	25	TNTC	115	Moribund
	XR Infected	6628	0	TNTC	115	Moribund
	XR Infected	6629	2			Healthy
	XR Infected	6630	0	TNTC	96	Moribund
	XR Infected	6631	0	TNTC	115	Moribund
	XR Infected	6632	0			Healthy
yes	XR Infected	6633	0			Healthy

TNTC= Too numerous to count

XR= Irradiation
RBM= Rules-Based Medicine

In an additional experiment, 48 animals were pouched (see data in Table 7). The following day, 44 mice received an irradiation dose of 413 rads each and 4 mice were not irradiated. Six days after the pouches were created, 44 mice had good pouches. Thirty-five XR mice were injected with 1.5×10^6 CFU E.coli bort. Four non-XR mice were injected, and nine XR mice were not injected. The data obtained by RBM for the animals in this experiment are shown in Appendix A (Experiment f).

Table 7

Sent to RBM 22hr Sample	Sent to RBM Euthanasia Sample	Treatment	Animal Number	CFU/25ul Blood at 22h	Time at Euthanasia (hr)	CFU/25ul Blood at 22h	Health Status at Euthanasia
		Non-XR, Infected	7315	48			Healthy
		Non-XR, Infected	7316	0			Healthy
		Non-XR, Infected	7317	2			Healthy
		Non-XR, Infected	7318	0	144		Moribund
yes	yes	XR, Infected	7319	1	68	TNTC	Moribund
yes	yes	XR, Infected	7320	0	92	TNTC	Moribund
		XR, Infected	7321	3	92	TNTC	Moribund
yes	yes	XR, Infected	7322	0	98	TNTC	Moribund
yes		XR, Infected	7323	0			Healthy
		XR, Infected	7324	0	172		Moribund
		XR, Infected	7325	3	172	TNTC	Moribund
		XR, Infected	7326				Healthy
yes		XR, Infected	7327	84			Healthy
		XR, Infected	7328	86	126		Moribund
yes		XR, Infected	7329	1			Healthy
yes	yes	XR, Infected	7330	1	98	TNTC	Moribund
		XR, Infected	7331	3	76	TNTC	Moribund
yes		XR, Infected	7332	2			Healthy
yes		XR, Infected	7333	1			Healthy
yes	yes	XR, Infected	7334	0	68	TNTC	Moribund
		XR, Infected	7335	2	126		Moribund
		XR, Infected	7336	0			Healthy
yes		XR, Infected	7337	0			Healthy
		XR, Infected	7338	130	68		Moribund

		XR, Infected	7339				Healthy
		XR, Infected	7340	70	212		Moribund
yes	yes	XR, Infected	7341	0	98	TNTC	Moribund
		XR, Infected	7342	0	126	TNTC	Moribund
		XR, Infected	7343	0	146	TNTC	Moribund
		XR, Infected	7344	13	98	TNTC	Moribund
yes	yes	XR, Infected	7345	1	76	TNTC	Moribund
yes		XR, Infected	7346	0			Healthy
		XR, Infected	7347	0	212		Moribund
yes		XR, Infected	7348	0			Healthy
		XR, Infected	7349	0	144	TNTC	Moribund
yes	yes	XR, Infected	7350	0	76	TNTC	Moribund
		XR, Infected	7351	0	212		Moribund
		XR, Infected	7352	9	126		Moribund
		XR, Infected	7353	7	68		Moribund
yes		XR, Non-Infected	7354	0			Healthy
yes		XR, Non-Infected	7355	0			Healthy
		XR, Non-Infected	7356	0			Healthy
yes		XR, Non-Infected	7357	0			Healthy
yes		XR, Non-Infected	7358	0			Healthy
yes		XR, Non-Infected	7359	0			Healthy
yes		XR, Non-Infected	7360	0			Healthy
yes		XR, Non-Infected	7361	0			Healthy
yes		XR, Non-Infected	7362	0			Healthy

The resulting data indicate that the survival rate for animals that were not irradiated, but were infected (with from 1.5-1.8x10^6 CFU/mouse) was 94% (15/16). The survival rate for animals that were irradiated, (from 385 to 424 rads) but were not infected was 100%. The survival rate at Day 8 for animals that were infected and also irradiated (infection with 1.5-1.8x10^6 CFU/mouse and irradiation from 385 to 424 rads) varied from 30 to 57%. The moribund animals that were euthanized and tested for the presence of bacteria in their blood were all found to have had bacteremia at the time of euthanasia.

Example 2 – Identification of a Biomarker Panel in an Immunocompromised Mouse Model at 22 Hours Post-Infection

In an experiment using mice immunocompromised as described above, 22 mice were tested. Of these animals, 8 were doomed and 8 survived. As described in the survival study

in Example 1, blood samples were taken from mice at 22 hours after infection. These samples were analyzed and used to derive a model to predict the outcome, i.e., survived or doomed, for animals that were both irradiated and infected with bacteria.

The 59 analytes measured in the samples were Apolipoprotein A1, β2 Microglobulin, C Reactive Protein, D-dimer, EGF, Endothelin-1, Eotaxin, Factor VII, FGF-9, FGF-Basic, Fibrinogen, GCP-2, LIX, GM-CSF, Growth Hormone, GST, Haptoglobin, IFN-α, IgA, IL-10, IL-11, IL-12p70, IL-17, IL-18, IL-1α, IL-1ß, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, Insulin, IP-10, KC-GRO, Leptin, LIF, Lymphotactin, MCP-1-JE, MCP-3, MCP-5, M-CSF, MDC, MIP-1α, MIP-1ß, MIP-1α, MIP-2, MIP-3ß, Myoglobin, OSM, RANTES, SCF, SGOT, TIMP-1, Tissue Factor, TNF-α, TPO, VCAM-1, VEGF, and VWF. These analytes were found to be predictive of death versus survival in the mouse model.

Identification of a panel of six biomarkers predictive of survival vs. death was accomplished as described below. First, the data were transformed to the log scale (natural base). T-tests were performed on the dataset, for each analyte, to determine which analytes were present at statistically-significantly different concentrations between doomed animals and survived animals at the 22-hour timepoint. A total of 13 analytes were selectable at the significance level 0.05, and 6 analytes were selectable at the significance level 0.02.

Next, the performance, in terms of discriminating between survived and doomed animals, of the 13 analytes and the 6 analytes was checked by principle component analysis. Both subsets of analytes showed similar performance, so the 6 analytes were chosen as the final discrimination marker. They were: MCP-1-JE, IL-6, MCP-3, IL-3, MIP-1β, and KC-GRO. The raw data obtained using the 6 analytes are shown in Table I.

Then, a discrimination function using the 6 analytes was derived using a two-step technique. First, a principle component analysis performed on the 6 analytes showed that only the first 2 principle components (each a linear combination of the original 6 analytes) were needed to explain more than 96% variation in the original data. Therefore, the dimensionality of the data was reduced from 6 to 2. Linear discriminant analysis (LDA) was then performed on the 2 principle components, giving the best linear combination of the 2 principle components in terms of maximizing the difference between doomed and survived animals.

The end product of the above analysis was a linear combination of the original 6 analytes, which was used to assign a score for each animal. Score = 19(MCP-1-JE) + 27(IL-6) + 18(MCP-3) + 21(IL-3) + 18(MIP-1ß) + 25(KC-GRO).

A threshold was set which gave a 100% correct prediction of doomed animals, resulting in an 87.5% correct prediction of survived animals.

Example 3 – Use of Biomarker Panel Identified in Immunocompromised Mouse Model to Predict Disease Outcome - I

The discrimination function derived as described in Example 2 was applied to a set of mice. The discrimination model correctly predicted 100% doomed and 100% survived animals.

Example 4 – Use of Biomarker Panel Identified in Immunocompromised Mouse Model to Predict Disease Outcome - II

The discrimination function derived as described in Example 2 was further applied to another set of mice. In this case, the discrimination model correctly predicted 100% doomed and 62.5% survived animals.

Example 5 – Identification of a Biomarker Panel at Selected Timepoints Post-Infection

The results described in Examples 1- 4 showed that in this mouse model, the level of analytes measured in plasma collected at 22 hours post-infection was predictive of death vs. survival. To expand on these findings and determine whether the set of analytes identified at 22-hours post infection would be predictive of death risk when analyte levels were measured at different timepoints after onset of infection, a time-course experiment was performed, sampling blood at 4, 10, 24, 48, and 96 hours post infection. Because a single animal should not be bled five times, an experiment was designed in which many animals were used and bled only once. To ensure an even distribution of samples in the two groups, survivor vs. doomed, conditions were selected that resulted in >90% survival or >90% death. For the survivor group, infected, non-irradiated mice were used. The experiments described above (see Table 3) showed that irradiated and infected animals that survived had an analyte profile similar to animals that were infected and non-irradiated. For the doomed group, higher doses of irradiation and infection were used, which had previously shown to be lethal to more than 90% of animals.

A total of 156 C3H/HeN mice were used in this experiment. Animals were divided into six treatment groups as shown in Table 8. Group 1: non-pouched, non-irradiated, non-infected (15); Group 2: pouched, non-irradiated, non-infected (14); Group 3: pouched, non-

irradiated, infected (36); Group 4: non-pouched, irradiated, non-infected (12); Group 5: pouched, irradiated, non-infected (14); Group 6: pouched, irradiated, infected (65).

Table 8

Group #	1	2	3	4	5	6
Treatment		Pouch	Pouch and Infection	XR	XR-Pouch	XR-Pouch and Infection
number of mice	15	14	36	12	15	65

Mice were pouched and irradiated (450 rads) 24 hours later. Five days after irradiation, mice were infected with a100-μl bacterial suspension containing 2.2 x 10^6 CFU of *E. coli* Bort/mouse. As shown in Table 9, mice were sacrificed and bled at the selected times. Before each timepoint, animals that were deemed too sick to survive until the next time point were euthanized. These samples were labeled "d" or "F," where F indicates animals appearing to be sicker than d animals. After removing these sick animals, four to seven animals from the infected and four to seven from the infected and irradiated groups were euthanized. Control animals (non-infected) were euthanized at 0, 48, and 96 hours post infection. Sample collection was terminated at 96 hours after infection. Blood samples were divided into aliquots. One aliquot of 20 μl was used for bacterial counts. A second aliquot of 100 μl was concentrated by centrifugation and plasma was collected, divided into two aliquots, and stored frozen.

Table 9

	NO-XR						XR-450					
Group	1		2		3		4		5		6	
Treatment	no Pouch		Pouch		Pouch and Infection		no Pouch		Pouch		Pouch and Infection	
Hours after Infection	#of mice	an. #	# of mice	an. #	# of mice	an. #	# of mice	an. #	# of mice	an. #	# of mice	an. #
0	5	1-5	4	10-13			4	6-9	4	14-17		
4					6	18-23					7	24-30
10					6	37-42					6	31-36
24					5	43-47					6	48-53
48	5	64-68	5	69-73	5	54-58 3d	4	79-82	5	74-78	5	59-63 1d,2d,4d 1-5F
72					4	84-87					5	88-92 5-7d, 6-8F
96	5	119-123	5	105-109	5	93-97	4	115-118	5	110-114	7	98-104 9-12F

Selected plasma samples (Table 10) were sent to RBM for analyte determination. The rest of the blood, 300-500 µl was added to 4.5 ml of RNA Wiz for RNA isolation and stored at –80°C.

Table 10

Euthanized Hours post infection	XR	An #	Bacterial counts CFU/ml
0	-	**1**	0.0E+00
0	-	**2**	0.0E+00
0	-	**3**	0.0E+00
0	-	**4**	0.0E+00
0	+	**6**	0.0E+00
0	+	**7**	0.0E+00
0	+	**8**	0.0E+00
0	+	**9**	0.0E+00

Table 10

Euthanized Hours post infection	XR	An #	Bacterial counts CFU/ml
48	-	**54**	5.6E+02
48	-	**55**	4.0E+04
48	-	**56**	8.0E+02
48	-	**57**	5.0E+03
48	-	**58**	2.4E+02
48	+	**59**	8.0E+03
48	+	**60**	4.0E+01
48	+	**61**	1.2E+02

0	-	**10**	0.0E+00
0	-	**11**	0.0E+00
0	-	**12**	0.0E+00
0	-	**13**	0.0E+00
0	+	**14**	0.0E+00
0	+	**15**	0.0E+00
0	+	**16**	0.0E+00
0	+	**17**	0.0E+00
4	-	**18**	0.0E+00
4	-	**19**	0.0E+00
4	-	**20**	0.0E+00
4	-	**21**	0.0E+00
4	-	**22**	0.0E+00
4	-	**23**	0.0E+00
4	+	**26**	0.0E+00
4	+	**27**	0.0E+00
4	+	**28**	0.0E+00
4	+	**29**	0.0E+00
4	+	**30**	0.0E+00
10	+	**31**	0.0E+00
10	+	**32**	0.0E+00
10	+	**33**	0.0E+00
10	+	**34**	0.0E+00
10	+	**36**	2.8E+02
10	-	**37**	0.0E+00
10	-	**39**	0.0E+00
10	-	**40**	0.0E+00
10	-	**41**	0.0E+00
10	-	**42**	0.0E+00
24	-	**43**	4.0E+04
24	-	**44**	0.0E+00
24	-	**45**	0.0E+00
24	-	**46**	0.0E+00
24	-	**47**	0.0E+00
24	+	**48**	0.0E+00
48	+	**62**	4.0E+01
48	+	**63**	4.0E+01
72	-	**84**	0.0E+00
72	-	**85**	0.0E+00
72	-	**86**	0.0E+00
72	-	**87**	0.0E+00
72	+	**88**	0.0E+00
72	+	**89**	0.0E+00
72	+	**90**	6.0E+08
72	+	**91**	2.0E+04
72	+	**92**	0.0E+00
96	-	**93**	0.0E+00
96	-	**94**	0.0E+00
96	-	**95**	0.0E+00
96	-	**96**	0.0E+00
96	-	**97**	0.0E+00
96	+	**98**	2.0E+08
96	+	**99**	2.0E+03
96	+	**100-101**	0.0E+00
96	+	**102**	0.0E+00
96	+	**103**	1.3E+08
96	+	**104**	2.0E+06
48	+	**1d**	2.6E+09
48	+	**2d**	2.2E+09
48	-	**3d**	TNTC*
72	+	**5d**	1.2E+09
48	+	**1F**	7.0E+07
48	+	**2F**	5.0E+08
48	+	**3F**	3.0E+06
48	+	**4F**	8.0E+08
48	+	**5F**	1.0E+08
72	+	**6F**	8.0E+08
72	+	**7F**	6.0E+08
72	+	**8F**	6.0E+08
96	+	**9F**	5.0E+08

24	+	**49**	0.0E+00
24	+	**50**	0.0E+00
24	+	**51**	0.0E+00
24	+	**52**	0.0E+00
24	+	**53**	TNTC*

96	+	**10F**	1.2E+09
96	+	**11F**	2.2E+09

* TNTC = too numerous to count

Appendix D shows the level of analytes for plasma samples obtained at different time points after infection. These data were analyzed using different statistical approaches, described below.

The statistical analyses and figures, unless indicated otherwise, were produced using the statistical software available from the R Project For Statistical Computing at http://www.r-project.org, Ihaka et al.,1996, *Journal of Computational and Graphical Statistics* and Insightful S-plus® software (http://www.insightful.com/products/splus/default.asp).

A two-way analysis of variance (ANOVA) model was used to fit data for each analyte considering time and treatment group as two factors. The simplest ANOVA model is one-way ANOVA, which may be employed if it is desirable to determine if all the means from multiple different groups are equal (i.e., one factor with multiple levels). When only two groups (i.e., one factor with 2 levels), the ANOVA approach reduces to a simple t-test approach.

This approach may be extended to multifactor analysis. In the present analysis, two factors were considered: time, which has 7 levels (i.e., 7 timepoints), and treatment group, which has 2 levels (i.e., animal groups). In a two-way ANOVA analysis, the effects of two factors are tested separately (their main effects) and (sometimes) together (their interaction effect). If the interaction effect between time and treatment group for a particular analyte is significant (if the interaction p value < 0.05), this is interpreted to indicate that the time-profiles of this analyte are significantly different between the two treatment groups. The p values corresponding to the main effects and interaction effect from the ANOVA analysis are listed in the Table 11 below. Analyte measurements of zero were replaced by 0.001; all measurement values were log based 2 transformed before fitting the model.

Table 11

Analytes	time Main effect p value	group Main effect p value	time*group Interaction p value
KC...GROalpha	0.000	0.000	0.000
IL.6	0.000	0.001	0.000

TIMP.1	0.000	0.604	0.000
IL.3	0.000	0.003	0.001
IL.5	0.001	0.011	0.001
Fibrinogen	0.000	0.046	0.001
M.CSF	0.052	0.004	0.005
VCAM.1	0.000	0.000	0.005
TPO	0.014	0.377	0.006
IL.1alpha	0.015	0.056	0.006
GCP.2...LIX	0.011	0.546	0.007
IL.10	0.378	0.004	0.014
MIP.2	0.000	0.003	0.015
IL.1beta	0.138	0.907	0.016
TF	0.011	0.049	0.017
MCP.3	0.000	0.000	0.019
VEGF	0.008	0.023	0.024
RANTES	0.000	0.003	0.027
IL.18	0.000	0.430	0.027
OSM	0.032	0.000	0.031
MIP.1.alpha	0.161	0.152	0.035
Haptoglobin	0.000	0.092	0.036
IL.11	0.004	0.022	0.046
MIP.1.beta	0.000	0.011	0.055
MCP.1...JE	0.000	0.000	0.069
MIP.1gamma	0.000	0.641	0.078
FGF.9	0.002	0.002	0.085
MCP.5	0.000	0.000	0.090
Leptin	0.154	0.000	0.111
IgA	0.015	0.006	0.136
vWF	0.001	0.452	0.146
MDC	0.000	0.000	0.183
IL.12p70	0.110	0.519	0.215
IP.10	0.000	0.013	0.220
IFN.g	0.000	0.040	0.229
Apolipoprotein.A1	0.000	0.863	0.243
Endothelin.1	0.018	0.068	0.275
IL.4	0.075	0.018	0.291
Factor.VII	0.011	0.062	0.322
IL.17	0.013	0.119	0.379
SCF	0.116	0.010	0.401
LIF	0.564	0.013	0.437
IL.7	0.215	0.662	0.438
GM.CSF	0.629	0.203	0.463
FGF.basic	0.001	0.008	0.474
C.Reactive.Protein	0.045	0.905	0.484
IL.2	0.190	0.395	0.506
Lymphotactin	0.150	0.026	0.530
GST	0.163	0.853	0.532
SGOT	0.110	0.516	0.540
MIP.3beta	0.512	0.119	0.540
Growth.Hormone	0.332	0.066	0.622
EGF	0.046	0.056	0.743
TNF.alpha	0.020	0.002	0.760
Myoglobin	0.016	0.706	0.828
Insulin	0.004	0.000	0.917
Eotaxin	0.181	0.001	0.941

The time-profiles of each analyte are also graphically represented in standard and log2-transformed formats (Figures 1A-1C and Figures 2A-2D, respectively). The results show that, among the analytes tested, fibrinogen, GCP2/LIX, haptoglobin, IL-10, IL-11, IL-18, IL-1α, IL-1β, IL-3, IL-5, IL-6, KC-GROα, M-CSF, MIP-1a, MIP-2, OSM, RANTES, TIMP1, TF, TPO, VCAM1, and VEGF had an interaction p value< 0.05.

The analyte measurements were further analyzed to determine linear trend differences between the INFECTED and XR.INFECTED groups. Each analyte measurement for each group was summarized across each timepoint and assigned a score. The scores for each analyte were then compared between the two treatment groups. The procedure for the data analysis is described in more detail below.

More particularly, measurements of zero are replaced with 0.01, and all the data then log2 transformed. Letting $x_{t,i,l}$ represent an analyte measurement at time t, taken from i^{th} animal in treatment group l, the mean analyte measurement at time t is calculated as

$y_{t\bullet l} = \frac{\sum_{i} x_{til}}{n}$, where n is number of animals at time t of group l. Letting

$score1 = y_{4\bullet 1} + y_{10\bullet 1} + y_{24\bullet 1} + y_{48\bullet 1} + 2\times y_{72\bullet 1} + 2\times y_{96\bullet 1} - 8\times y_{0\bullet 1}$, then the variance of $score1$ is calculated,

$$\mathrm{var}(score1) = \mathrm{var}(y_{4\bullet 1}) + \mathrm{var}(y_{10\bullet 1}) + \mathrm{var}(y_{24\bullet 1}) + \mathrm{var}(y_{48\bullet 1}) + 4\times \mathrm{var}(y_{72\bullet 1}) + 4\times \mathrm{var}(y_{96\bullet 1}) + 64\times \mathrm{var}(y_{0\bullet 1})$$

Then, the test statistics for comparing the difference in linear trend of the two treatment groups is $\frac{score1 - score2}{\sqrt{\mathrm{var}(score1) + \mathrm{var}(score2)}}$, which follows a t distribution with 76 degrees of freedom under the null hypothesis. The results are shown in Table 12 below.

Table 12

Analytes	*Test statistics*	*Trend difference P value*	*ANOVA Interaction.p*
KC...GROalpha	-6.11	3.96E-08	0.000164
OSM	-4.63	1.46E-05	0.0307
IL.6	-4.6	1.68E-05	0.000305
TIMP.1	-4.57	1.84E-05	0.0166
IL.3	-4.32	4.74E-05	0.00102
VEGF	-3.81	0.000283	0.0242
FGF.9	-3.77	0.000326	0.0846
MCP.1...JE	-3.52	0.000737	0.00483
IL.11	-3.43	0.000982	0.0457
IL.10	-3.11	0.00266	0.014
MCP.3	-3.05	0.00312	0.0693
MIP.2	-2.91	0.00468	0.0146
MIP.1.beta	-2.76	0.0072	0.0547
MIP.1.alpha	-2.54	0.013	0.035
MDC	-2.54	0.0131	0.183
RANTES	-2.5	0.0144	0.0265
IL.1beta	-2.47	0.0156	0.016
Haptoglobin	-2.38	0.0201	0.0361
Fibrinogen	-2.36	0.021	0.00145
MCP.5	-2.29	0.025	0.0192
MIP.1gamma	-2.27	0.026	0.0777
SCF	-2.23	0.0285	0.401
IgA	-2.14	0.0354	0.136

IP.10	-2.06	0.0432	0.22
IL.1alpha	-2.03	0.0459	0.00571
IL.7	-1.87	0.0657	0.438
TNF.alpha	-1.81	0.074	0.76
TPO	-1.77	0.0802	0.00564
IL.17	-1.75	0.0835	0.379
IFN.g	-1.72	0.0888	0.229
IL.2	-1.61	0.112	0.506
Factor.VII	1.59	0.115	0.322
Growth.Hormone	1.48	0.143	0.622
IL.18	-1.43	0.158	0.0271
Lymphotactin	-1.37	0.175	0.53
GM.CSF	-1.37	0.176	0.463
M.CSF	-1.28	0.205	0.0899
GCP.2...LIX	-1.21	0.231	0.00688
GST	1.16	0.249	0.532
IL.12p70	-1.15	0.255	0.215
Leptin	-0.932	0.354	0.111
Apolipoprotein.A1	-0.924	0.358	0.243
Myoglobin	-0.693	0.491	0.828
LIF	0.668	0.506	0.437
IL.5	0.615	0.54	0.0012
C.Reactive.Protein	-0.608	0.545	0.484
vWF	0.564	0.574	0.146
IL.4	-0.537	0.593	0.291
MIP.3beta	0.493	0.623	0.54
TF	-0.434	0.665	0.000404
VCAM.1	-0.408	0.684	0.00541
SGOT	0.324	0.747	0.54
Insulin	0.292	0.771	0.917
EGF	-0.269	0.788	0.743
Endothelin.1	-0.26	0.796	0.275
Eotaxin	0.257	0.798	0.941
FGF.basic	0.167	0.868	0.474

Analytes that displayed significant differences ($p < 0.1$) in their time-profile between the two treatment groups are shown in Figures 3A-3E.

Using another data-analysis or statistical approach, a principle component analysis (PCA) with the Galaxy data-visualization tool from OmniViz was also performed, representing the analyte values obtained for each animal rather than the average values calculated for the samples obtained at a selected timepoint. In this representation of data, each symbol represents the analyte levels for one animal. A Galaxy map is shown for six different groups of analytes. Results are shown in Figures 24A-24F. When the levels of all the analytes were considered (Figure 24A), the best separation between survivor and doomed groups resulted in five doomed animals in the survivors area and 9 survivors in the doomed area. In comparison, when the classical pro-inflammatory factors, TNFa, IL1b, and IL-6 were used (Figure 24B), the separation between survivors and doomed misclassified nine survivor and six doomed animals. When the 14 analytes identified in Appendix were used (see Figure 24C), only two doomed animals were misclassified, and eleven survivors were found in the doomed area. According to the analytes that differentiate survivor from doomed

groups at 4 and 10 hours after infection (Figure 24D), six survivor and five doomed animals were misclassified. Removing KC and OSM from this analysis (Figure 24E) resulted in a better separation, which was further improved by the removal of IL-11. The best separation between survivors and doomed animals was achieved when MCP-1 and VEGF were used to estimate the risk of death (Figure 24F). In this case, all the doomed animals were assigned to an area where only eight survivors can be found. MCP-1 and VEGF were selected because both induce vascular permeability. It is postulated that that high plasma levels of VEGF and MCP-1 induce systemic microvascular permeability that results in multiple organ dysfunction and death.

Examination of interaction effect between INFECTED and XR.INFECTED groups at specific time points:

Here a similar two-way ANOVA analysis was used, but the factor of time had only two levels (x hours vs. 0 hr). Group, hour, and interaction p values are shown in Tables 13 through 18 below, for four hour vs. zero hour (Table 13), ten hours vs. zero hour (Table 14), 24 hour vs. zero hour (Table 15), 48 hours vs. zero hour (Table 16), 72 hours vs. zero hour (Table 17), and 96 hours vs. zero hour (Table 18). The corresponding standard box-and-whisker plots of the data presented in Tables 13 through 18 are depicted in Figure 4 through Figure 9, respectively.

Table 13

4 hours vs. 0 hour (ranked by the interaction p value)

	group.P	hour.P	interaction.P
KC...GROalpha	0.0372	2.14E-20	0.000221
OSM	0.033	0.00829	0.000648
IL.3	0.692	0.000532	0.00165
MIP.2	0.0498	1.88E-08	0.00937
MIP.1.beta	0.187	5.75E-05	0.0105
MCP.1...JE	2.84E-05	5.84E-10	0.0119
GST	0.554	0.884	0.0127
VEGF	0.254	0.112	0.0435
IL.11	0.166	0.00673	0.0438
TIMP.1	0.00306	0.00896	0.0493
IL.5	0.141	0.153	0.0587
LIF	0.0237	0.404	0.0636
MCP.3	5.41E-05	3.98E-09	0.0684
Haptoglobin	0.0519	0.00719	0.0763
Apolipoprotein.A1	0.923	0.506	0.104
SCF	0.453	0.301	0.12
IP.10	0.769	6.51E-09	0.163

IL.6	0.447	4.05E-16	0.172
RANTES	0.273	2.52E-05	0.196
IL.1beta	0.126	0.19	0.198
Endothelin.1	0.0223	0.688	0.199
IL.10	0.654	0.00353	0.208
TNF.alpha	0.294	0.0651	0.209
FGF.9	0.408	0.00103	0.234
MDC	2.90E-05	0.782	0.234
MCP.5	0.127	0.000102	0.237
M.CSF	0.00228	0.142	0.323
MIP.3beta	0.272	0.965	0.356
Factor.VII	0.716	0.982	0.373
Growth.Hormone	0.911	0.976	0.419
Leptin	0.000496	0.303	0.466
SGOT	0.658	0.795	0.473
Lymphotactin	0.511	0.409	0.523
GM.CSF	0.958	0.285	0.537
IL.4	0.597	0.46	0.539
IgA	8.66E-05	0.0369	0.544
IL.7	0.279	0.14	0.548
Eotaxin	0.0119	0.565	0.559
vWF	0.149	0.495	0.579
Fibrinogen	0.343	0.0634	0.584
MIP.1.alpha	0.06	0.694	0.587
IL.12p70	0.847	0.0761	0.605
MIP.1gamma	0.576	0.351	0.611
Myoglobin	0.182	0.441	0.696
IFN.g	0.607	0.746	0.702
VCAM.1	1.78E-05	0.133	0.733
GCP.2...LIX	0.304	0.0687	0.742
EGF	0.0489	0.857	0.756
FGF.basic	0.267	0.827	0.766
Insulin	0.104	0.0205	0.766
IL.17	0.313	0.0343	0.767
C.Reactive.Protein	0.578	0.981	0.834
TPO	0.068	0.198	0.836
IL.1alpha	0.405	0.000689	0.86
IL.18	0.385	0.327	0.872
IL.2	0.171	0.00373	0.96
TF	0.341	0.897	0.973

Table 14

10 hours vs. 0 hour (ranked by the interaction p value)

	group.P	*hour.P*	*interaction.P*
OSM	0.0137	0.000255	0.000306
M.CSF	0.228	0.843	0.000995
VEGF	0.947	9.07E-06	0.00158
Lymphotactin	0.00911	0.000409	0.00394
IL.11	0.659	0.00326	0.00698
FGF.9	0.0535	4.58E-06	0.0171
IP.10	0.138	3.49E-08	0.0182
KC...GROalpha	0.0855	1.15E-16	0.0328
MCP.1...JE	0.000118	6.88E-11	0.046
MIP.1gamma	0.832	1.10E-06	0.0496
MIP.1.beta	0.405	4.33E-09	0.0505
IgA	0.00239	0.19	0.0862
SCF	0.373	0.0108	0.0902
MIP.1.alpha	0.16	0.000336	0.0941
VCAM.1	8.78E-06	0.000811	0.103
Haptoglobin	0.025	4.33E-05	0.111
IL.1beta	0.147	0.00438	0.121
IL.2	0.909	0.235	0.123
IL.3	0.149	3.03E-08	0.138
TNF.alpha	0.215	0.00555	0.146
Apolipoprotein.A1	0.724	0.708	0.159
MIP.2	0.251	1.86E-09	0.178
GST	0.697	0.346	0.207
Endothelin.1	0.806	0.714	0.245
MDC	0.000406	0.00173	0.249
IL.18	0.827	0.00552	0.278
IL.10	0.642	0.00441	0.381
Growth.Hormone	0.928	0.522	0.408
Insulin	0.0139	0.691	0.42
IL.12p70	0.228	0.0361	0.425
MIP.3beta	0.795	0.162	0.436
IL.1alpha	0.836	0.000752	0.469
IL.4	0.608	0.0628	0.491
SGOT	0.573	0.766	0.505
Fibrinogen	0.962	2.90E-06	0.518
GM.CSF	0.362	0.185	0.526
IL.6	0.154	2.39E-16	0.531
MCP.5	0.195	5.66E-08	0.534
Eotaxin	0.118	0.504	0.602
TIMP.1	1.15E-05	4.23E-08	0.62
IL.17	0.747	0.000555	0.621
LIF	0.591	0.867	0.64
Leptin	0.00398	0.502	0.677
IL.7	0.222	0.000626	0.684
GCP.2...LIX	0.44	0.00794	0.698

RANTES	0.556	4.35E-09	0.728
MCP.3	0.000606	4.05E-09	0.741
Factor.VII	0.514	0.779	0.759
Myoglobin	0.524	0.178	0.775
FGF.basic	0.257	0.373	0.799
IFN.g	0.751	0.0132	0.857
IL.5	0.939	0.0538	0.862
vWF	0.334	0.0528	0.889
TF	0.282	0.346	0.918
C.Reactive.Protein	0.754	0.431	0.923
EGF	0.103	0.621	0.945
TPO	0.0763	0.027	0.978

Table 15

24 hours vs. 0 hour (ranked by the interaction p value)

	group.P	*hour.P*	*interaction.P*
IL.5	0.0412	0.497	0.012
Leptin	0.0503	0.306	0.0304
TF	0.00827	0.464	0.0347
VEGF	0.805	0.0903	0.0387
Haptoglobin	0.0702	1.07E-06	0.0521
IL.11	0.604	0.516	0.0578
IL.10	0.569	0.653	0.0714
M.CSF	0.0177	0.507	0.0842
GCP.2...LIX	0.0207	0.0471	0.0994
IL.3	0.362	1.28E-07	0.103
IFN.g	0.225	0.0478	0.12
Factor.VII	0.475	0.115	0.134
TIMP.1	0.00271	1.20E-08	0.137
Growth.Hormone	0.552	0.149	0.144
MCP.1...JE	0.000169	3.17E-09	0.162
GST	0.729	0.193	0.214
FGF.basic	0.0727	0.366	0.245
Apolipoprotein.A1	0.708	0.94	0.26
SGOT	0.994	0.547	0.27
MDC	0.00039	1.23E-06	0.333
IL.6	0.546	1.59E-08	0.353
MCP.3	0.000152	4.30E-09	0.363
IL.18	0.228	0.016	0.387
SCF	0.728	0.798	0.39
Lymphotactin	0.301	0.0916	0.407
MCP.5	0.0923	3.82E-07	0.418
IP.10	0.651	8.25E-05	0.421

IL.17	0.859	0.0295	0.433
OSM	0.947	0.044	0.455
IL.2	0.689	0.382	0.469
Myoglobin	0.761	0.268	0.499
IL.4	0.0956	0.0231	0.506
C.Reactive.Protein	0.407	0.344	0.507
MIP.3beta	0.406	0.191	0.507
MIP.1.beta	0.904	0.117	0.519
MIP.1gamma	0.131	4.85E-09	0.533
VCAM.1	7.26E-09	0.0464	0.538
FGF.9	0.534	0.0157	0.539
TNF.alpha	0.556	0.912	0.542
vWF	0.207	0.192	0.572
LIF	0.21	0.215	0.579
GM.CSF	0.895	0.0992	0.587
Endothelin.1	0.0684	0.24	0.619
Eotaxin	0.0155	0.574	0.676
EGF	0.193	0.209	0.704
IL.1beta	0.015	0.0274	0.706
Fibrinogen	0.818	9.35E-08	0.72
KC...GROalpha	0.612	3.63E-05	0.733
IL.12p70	0.456	0.0729	0.756
MIP.2	0.589	2.25E-05	0.778
IL.7	0.272	0.226	0.782
MIP.1.alpha	0.0637	0.139	0.799
TPO	0.0523	0.015	0.826
RANTES	0.484	3.87E-07	0.866
IgA	0.000361	0.0323	0.92
IL.1alpha	0.546	0.0945	0.967
Insulin	0.0532	0.963	0.969

Table 16

48 hours vs. 0 hour (ranked by the interaction p value)

	group.P	*hour.P*	*Interaction.P*
TIMP.1	0.0139	3.14E-07	0.0319
IL.11	0.406	0.00626	0.0435
vWF	0.537	9.74E-06	0.0482
IL.17	0.423	0.00871	0.0809
Apolipoprotein.A1	0.99	0.000573	0.0867
Haptoglobin	0.0275	1.63E-05	0.122
EGF	0.692	0.539	0.153
C.Reactive.Protein	0.536	0.019	0.224
VCAM.1	0.000157	0.403	0.23

MIP.2	0.375	7.13E-08	0.231
IL.7	0.719	0.179	0.259
TNF.alpha	0.351	0.016	0.282
IL.1beta	0.133	0.0375	0.289
IL.2	0.844	0.0506	0.289
FGF.basic	0.0887	0.749	0.305
IL.3	0.153	1.84E-07	0.316
IL.10	0.967	0.554	0.336
OSM	0.822	0.0013	0.341
MIP.3beta	0.321	0.685	0.375
MIP.1.beta	0.233	1.91E-05	0.419
IL.12p70	0.945	0.0127	0.432
IFN.g	0.64	0.0122	0.442
Myoglobin	0.8	0.0555	0.446
Growth.Hormone	0.984	0.636	0.452
M.CSF	0.00221	0.0679	0.454
MCP.3	0.00168	1.11E-08	0.458
LIF	0.183	0.065	0.462
SGOT	0.147	0.0147	0.512
MIP.1gamma	0.287	0.0482	0.543
GM.CSF	0.893	0.159	0.547
Leptin	0.0047	0.326	0.549
Insulin	0.0157	0.111	0.561
IL.1alpha	0.781	0.0578	0.636
IL.6	0.97	5.25E-07	0.639
MIP.1.alpha	0.0531	0.0154	0.643
MCP.5	0.289	3.71E-08	0.669
IL.18	0.416	0.422	0.682
VEGF	0.101	0.0128	0.682
IL.4	0.558	0.0305	0.686
IL.5	0.817	0.125	0.712
Factor.VII	0.922	0.766	0.716
Lymphotactin	0.967	0.751	0.742
GCP.2...LIX	0.169	0.00102	0.743
Endothelin.1	0.177	0.133	0.78
RANTES	0.994	1.01E-05	0.787
Eotaxin	0.0179	0.00938	0.795
Fibrinogen	0.788	8.61E-08	0.801
MCP.1...JE	0.00247	1.01E-11	0.808
TF	0.383	0.0913	0.83
SCF	0.809	0.0154	0.849
IP.10	0.578	0.00035	0.861
MDC	2.35E-05	1.82E-07	0.905
GST	0.287	0.0487	0.92
IgA	0.0144	0.883	0.923
KC...GROalpha	0.939	4.04E-11	0.923

FGF.9	0.954	0.000459	0.941
TPO	0.0605	0.000942	0.98

Table 17

72 hours vs. 0 hour (ranked by the interaction p value)

	group.P	*hour.P*	*interaction.P*
KC...GROalpha	1.33E-05	2.09E-07	6.23E-07
Fibrinogen	0.0038	0.000758	9.33E-05
VCAM.1	0.00175	4.53E-05	0.000122
MIP.1gamma	0.058	0.0752	0.000361
IL.6	0.00692	4.70E-05	0.000445
IgA	0.289	0.000886	0.0017
TIMP.1	0.834	0.00142	0.00184
IL.3	0.268	0.0084	0.00215
MCP.3	1.84E-05	1.65E-05	0.00328
MCP.1...JE	4.19E-05	1.67E-07	0.00548
MIP.2	0.0373	0.00102	0.0153
VEGF	0.747	0.0105	0.0193
MCP.5	0.0134	0.000135	0.0237
FGF.9	0.0756	0.00105	0.0366
M.CSF	0.19	0.205	0.0408
OSM	0.26	0.0131	0.0493
MDC	0.0235	0.000216	0.0519
IFN.g	0.118	5.93E-05	0.052
IL.11	0.538	0.00533	0.0624
Haptoglobin	0.101	9.00E-06	0.0632
IL.18	0.387	0.0798	0.0693
RANTES	0.0843	0.000212	0.0734
MIP.1.beta	0.25	0.0156	0.0798
IP.10	0.268	4.60E-06	0.0875
Growth.Hormone	0.447	0.455	0.0925
GM.CSF	0.349	0.116	0.0979
GCP.2...LIX	0.716	0.0366	0.102
TPO	0.675	0.172	0.114
Factor.VII	0.3	0.229	0.12
MIP.1.alpha	0.504	0.106	0.124
SCF	0.376	0.637	0.13
IL.17	0.489	0.0129	0.137
IL.10	0.604	0.192	0.148
vWF	0.84	0.0485	0.153
IL.1alpha	0.583	0.223	0.157
C.Reactive.Protein	0.539	0.171	0.179
IL.12p70	0.602	0.203	0.207

TNF.alpha	0.298	0.0963	0.238
Lymphotactin	0.271	0.0968	0.275
IL.7	0.722	0.263	0.282
GST	0.666	0.02	0.287
IL.1beta	0.239	0.169	0.292
TF	0.908	0.0116	0.354
Myoglobin	0.949	0.00382	0.37
MIP.3beta	0.345	0.737	0.387
LIF	0.194	0.232	0.409
SGOT	0.175	0.274	0.454
IL.2	0.541	0.141	0.565
IL.4	0.17	0.152	0.595
Eotaxin	0.0968	0.155	0.62
Leptin	0.00498	0.0817	0.717
EGF	0.141	0.00248	0.758
Endothelin.1	0.224	0.019	0.825
FGF.basic	0.5	0.00328	0.841
Insulin	0.127	0.0559	0.844
Apolipoprotein.A1	0.147	0.00315	0.915
IL.5	0.82	0.0603	0.93

Table 18

96 hours vs. 0 hour (ranked by the interaction p value)

	group.P	*hour.P*	*interaction.P*
IL.10	0.0146	0.137	0.000593
OSM	0.0103	0.00177	0.000745
KC...GROalpha	0.00166	4.60E-09	0.000887
IL.6	0.00592	2.31E-05	0.000993
IL.3	0.143	2.10E-06	0.0011
TIMP.1	0.469	0.000107	0.00112
FGF.9	0.00365	8.90E-05	0.00131
IL.1beta	0.479	0.482	0.00156
TPO	0.361	0.289	0.00297
VEGF	0.284	0.00429	0.00306
IL.1alpha	0.0426	0.472	0.00343
IL.11	0.721	0.00491	0.00386
RANTES	0.00715	5.51E-06	0.0057
MDC	0.0292	0.000219	0.01
MIP.1.beta	0.0547	0.000329	0.0142
SCF	0.0906	0.0245	0.0193
MIP.1.alpha	0.124	0.0613	0.02
MCP.3	7.96E-05	9.32E-07	0.0208
MIP.2	0.0327	8.17E-05	0.0227
IL.7	0.47	0.31	0.0239
MCP.1...JE	0.00011	4.17E-09	0.026
MCP.5	0.00951	7.85E-07	0.0353
Fibrinogen	0.138	1.32E-07	0.0409
VCAM.1	1.43E-07	0.000631	0.0465
IL.18	0.305	0.0652	0.0509
IL.2	0.548	0.0591	0.0538
GCP.2...LIX	0.415	0.0372	0.0569
Leptin	0.0909	0.0948	0.061
Haptoglobin	0.0508	1.87E-06	0.0816

MIP.1gamma	0.753	0.0559	0.0826
IP.10	0.266	1.83E-05	0.0892
IFN.g	0.14	5.24E-06	0.0944
IL.12p70	0.341	0.024	0.109
IL.17	0.363	0.00106	0.116
IL.4	0.0196	0.0709	0.12
TNF.alpha	0.154	0.00541	0.141
Factor.VII	0.32	0.00339	0.16
GM.CSF	0.382	0.185	0.161
TF	0.89	0.028	0.175
Endothelin.1	0.843	0.25	0.22
IgA	0.0532	0.95	0.254
M.CSF	0.000516	0.361	0.307
FGF.basic	0.808	0.00353	0.353
SGOT	0.787	0.745	0.372
IL.5	0.46	0.342	0.442
LIF	0.683	0.234	0.523
Lymphotactin	0.382	0.00309	0.574
MIP.3beta	0.956	0.635	0.579
vWF	0.167	0.173	0.604
Insulin	0.0389	0.595	0.614
Apolipoprotein.A1	0.0535	1.87E-05	0.632
Growth.Hormone	0.814	0.328	0.646
Myoglobin	0.635	0.0268	0.692
EGF	0.117	0.865	0.747
Eotaxin	0.0362	0.234	0.783
GST	0.283	0.049	0.933
C.Reactive.Protein	0.65	0.409	0.975

Example 6 – Evaluation of Analytes and Biomarker Panel Identified in Mice Using Visualization Analysis

Data obtained from analyte measurements were assessed using OmniViz software for Galaxy map visualization analysis. This analysis was performed using an OmniViz Galaxy map to evaluate whether analytes distinguished between groups of animals having different disease outcomes.

Example 7 - Immunocompromised Mouse Model of Contained Infection Used for Validation of Potential Drug Targets and Testing of Therapeutic Compounds

In order to test therapies intended at controlling systemic inflammatory response rather than the infection, it is desirable to control the infection to avoid problems that can derive from a high bacterial load. To this end we controlled the infection by using antibiotics. In this experiment, a subcutaneous pouch was induced in C3H/HeN animals. On the following day, all mice were irradiated with 490 rads--a dose of irradiation that in previous experiments was shown to be associated with 100% mortality. At Day 6 after induction of the pouches, mice were infected with 4.5×10^6 CFU/mouse. As animals became sick (as detected by a ruffled fur), each animal was assigned to one of two different groups, *i.e.* a group to be treated with 0.3mg/mouse of ceftriaxone and a group to stay untreated. Thirteen animals did not receive any treatment and 21 were treated. Once an animal was assigned to

the treated group, it received a daily injection of antibiotic until the animal succumbed to death. Appendix C shows the survival curves for the 2 animal groups. The upper curve shows the data obtained using the antibiotic-treated animals, and the lower curve corresponds to the untreated animals. At death, spleens were removed from the animals, homogenized in PBS, and the CFU determined. Table 19 (Experiment g) shows the bacterial counts obtained for the animals that remained untreated as compared to count for the treated animals.

The bacterial counts in the spleens of treated animals are about 3 logs of magnitude lower than in the untreated animals. The conditions employed should therefore be useful for testing therapies to prevent the progression from sepsis to septic shock in the absence of overwhelming bacterial infection.

Table 19

Ceftriaxone 0.3mg/mouse	CFU/spleen	Ceftriaxone 0.3mg/mouse	CFU/spleen
NO	1.40E+08	YES	1.20E+04
NO	2.80E+07	YES	2.00E+03
NO	ND	YES	8.00E+05
NO	2.00E+06	YES	4.00E+04
NO	8.00E+06	YES	6.00E+06
NO	3.60E+08	YES	2.60E+04
NO	2.40E+08	YES	3.00E+03
NO	1.80E+08	YES	8.00E+03
No	3.00E+07	YES	8.00E+05
NO	1.60E+08	YES	1.80E+04
NO	3.00E+08	YES	6.00E+02
NO	1.60E+07	YES	a
NO	1.80E+08	YES	a
Average	1.37E+08	YES	a
		YES	a
		YES	a
		YES	a
		YES	a
		YES	a
		YES	a
		Average	7.01E+05

Example 8: Immunocompromised Mouse Model of Contained Infection Used for Assessment of Potential Treatments Aimed at Providing Survival Advantage Under Conditions of Sepsis/Septic Shock

The experiments outlined in Example 7 show that treatment with an antibiotic such as ceftriaxone can contain infection derived from high bacterial load in the immunocompromised mouse model. The experiments outlined below were performed to determine the ability of several different treatments to confer a survival advantage to mice in the context of the immunocompormised, infection-contained background.
The following general experimental procedure was employed in all of the experiments with potential sepsis treatments described in this example.

Mice were pouched six days and irradiated five days before infection. Eight- to 12-week-old C3H/HeN mice were anesthetized with isofluorane and wiped with alcohol in the area caudal to their ears. Pouches were created at this site by subcutaneous injection of 2-3 ml of air, followed by the subcutaneous injection of 0.2 ml of a 0.5% solution of croton oil in olive oil. Twenty-four hours later, mice were irradiated using a gamma irradiator. Five days after irradiation, animals were infected with *E. coli* strain Bort by direct injection of the bacterial suspension into the pouches. After infection, animals were treated as described for each individual experiment. Animals were checked daily for signs of pain and distress, including diarrhea, lethargy, ruffled fur, lack of appetite, and poor body condition. Animals were euthanized when they became very lethargic and unable to move when touched. It was previously determined that when mice reach such conditions they will die within 6-8 hours.

Testing with ethyl pyruvate:

It is known that ethyl pyruvate (EP) improves survival in animal models of cecal ligation and puncture (CLP)-induced sepsis and mesenteric ischemia-reperfusion. Ethyl pyruvate is also known to be an antioxidant, a reactive oxygen species scavenger, and an anti-inflammatory agent by virtue of its ability to inhibit NF-kB activation. Treatment with ethyl pyruvate and ceftriatxone was tested for its ability to confer a survival advantage in the immunocompromised mouse model.

Mice were pouched and irradiadiated as described above. The mice were assigned to four different groups: (1) ten mice were untreated (control mice); (2) nineteen mice were treated with 0.1mg/mouse of ceftriaxone (CEF) once every 24 hours for days (saline control mice); (3) twenty mice were treated with 0.1 mg/mouse ceftriaxone and 35 mg/ml ethyl

pyruvate once every 24 hours for four days (EP mice); and (4) ten mice were treated as for group (3) and received an additional injection of 35 mg/ml of EP at 30 and 54 hour timepoints (EP 2x mice). The data provided in Table 20 below and depicted in Figure 10 indicate that treatment with ethyl pyruvate confers a significant survival advantage to immunocompromised, infected mice relative to nontreated or CEF-treated controls.

Table 20

Group No	Bad	Treatment	Bacterial Counts	Status	Time death	Status.dead
1	0	No	4.0E+08	1	30	DEAD
1	0	No	1.3E+05	1	38	DEAD
1	0	No	2.5E+05	1	38	DEAD
1	0	No	2.2E+04	1	54	DEAD
1	0	No	3.0E+04	1	54	DEAD
1	0	No	4.2E+04	1	54	DEAD
1	0	No	5.0E+04	1	54	DEAD
1	0	No	6.4E+04	1	54	DEAD
1	0	No	1.0E+05	1	54	DEAD
1	0	No	1.0E+05	1	54	DEAD
2	0	Saline	1.0E+05	1	38	DEAD
2	0	Saline	2.0E+05	1	38	DEAD
2	0	Saline	2.3E+04	1	48	DEAD
2	0	Saline	2.5E+04	1	48	DEAD
2	0	Saline	3.0E+04	1	48	DEAD
2	0	Saline	8.0E+04	1	48	DEAD
2	1	Saline	8.0E+04	1	48	DEAD
2	0	Saline	1.6E+05	1	48	DEAD
2	0	Saline	3.0E+05	1	48	DEAD
2	0	Saline	7.0E+03	1	54	DEAD
2	0	Saline	1.1E+04	1	54	DEAD
2	0	Saline	1.5E+04	1	54	DEAD
2	0	Saline	1.6E+04	1	54	DEAD
2	0	Saline	1.8E+04	1	54	DEAD
2	0	Saline	3.4E+04	1	54	DEAD
2	0	Saline	1.0E+05	1	54	DEAD
2	0	Saline	2.7E+05	1	96	DEAD
3	0	EP	1.0E+04	1	48	DEAD
3	1	EP	3.0E+04	1	48	DEAD
3	0	EP	1.2E+05	1	48	DEAD
3	0	EP	2.0E+05	1	48	DEAD

3	0	EP	2.0E+05	1	48	DEAD
3	0	EP	3.0E+05	1	48	DEAD
3	0	EP	1.3E+04	1	54	DEAD
3	0	EP	2.5E+04	1	54	DEAD
3	0	EP	3.5E+04	1	54	DEAD
3	0	EP	6.5E+04	1	54	DEAD
3	0	EP	7.6E+04	1	54	DEAD
3	0	EP	.8.0E+04	1	54	DEAD
3	0	EP	2.0E+05	1	54	DEAD
3	1	EP	3.0E+05	1	54	DEAD
3	1	EP	1.2E+04	1	56	DEAD
3	1	EP	2.0E+03	1	78	DEAD
3	0	EP	1.6E+03	1	102	DEAD
3	0	EP	1.6E+03	1	168	DEAD
3	0	EP	1.6E+04	1	174	DEAD
3	0	EP	4.0E+04	0	174	ALIVE
4	0	EP 2x	2.0E+05	1	48	DEAD
4	0	EP 2x	5.0E+04	1	54	DEAD
4	0	EP 2x	3.0E+04	1	62	DEAD
4	0	EP 2x	5.0E+04	1	72	DEAD
4	0	EP 2x	1.0E+04	1	96	DEAD
4	0	EP 2x	1.7E+03	1	168	DEAD
4	0	EP 2x	3.0E+04	1	168	DEAD
4	0	EP 2x	0.0E+00	0	174	ALIVE
4	0	EP 2x	1.0E+03	0	174	ALIVE
4	0	EP 2x	2.4E+03	0	174	ALIVE

Treatment with anti-VEGF antibody:

VEGF is known to be a potent vascular permeability factor, inducing adema, hypotension via induction of iNOS, which results in the production of nitrous oxide (NO), and poor tissue perfusion. VEGF was also found to be elevated in doomed immunocompromised animals (see Figure 11).

To determine if high plasma levels of VEGF contribute to the morbidity of sepsis and lead to septic shock, four different experiments were carried out using the inventive mouse model. The protocols for each experiment are described below and summarized in Table 21.

Table 21: Experiments A, B, C, and D

Exp. A	24 hr.	48 hr.	72 hr.	96 hr.	120 hr.
Control Group (24)	Control Ab + Cef	Control Ab	Control Ab + Cef	Control Ab	

Treatment Group (21)	anti-VEGF + Cef	anti VEGF	anti-VEGF + Cef	anti-VEGF

Exp. B	24 hr.	48 hr.	72 hr.	96 hr.	120 hr.
Control Group (29)	1. Control Ab + Cef (10)	1. Control Ab	1. Control Ab	1. Control Ab	1. Control Ab
	2. Control Ab (19)	2. Control Ab + Cef	2. Control Ab	2. Control Ab	2. Control Ab
Treatment Group (31)	1. anti-VEGF + Cef (10)	1. anti-VEGF	1. anti-VEGF	1. anti-VEGF	1. anti-VEGF
	2. anit-VEGF (21)	2. anti-VEGF + Cef	2. anti-VEGF	2. anti-VEGF	2. anti-VEGF

Exp. C	4 hr.	48 hr.	72 hr.	96 hr.	120 hr.
Control Group (16)	Control Ab	Control Ab + Cef			
Treatment Group (16)	anti-VEGF	anti-VEGF + Cef			

Exp. D	12 hr.	36 hr.	72 hr.	96 hr.	120 hr.
Control Group (20)	Control Ab	Control Ab + Cef			
Treatment Group (20)	anti-VEGF	anti-VEGF + Cef			

Experiment A: Using the procedure described above, 45 mice were pouched, irradiated (495 rads) and infected (0.2 ml of 0.1 OD 600). The animals were randomly assigned to control and treatment groups. The animals in the treatment group received daily treatment with anti-VEGF antibody (goat anti-mouse VEGF neutralizing antibody; R&D Systems, Inc. Catalog# AF-493-NA), while the control group received daily treatment of isotype control antibody (starting at 24 hours and for 4 days). Antibodies were injected at the concentration of 250 μg/mouse. At 24 and 72 hours, injected solutions contained ceftriaxone to yield a dose of 100 μg/mouse. Animals were bled at 24 hours after infection and before treatment. Blood was used to determine bacterial counts and to prepare plasma. Plasma aliquots were stored at –80C. The results are provided in Table 22 and are graphically represented in Figures 12A-12D. The survival difference between the control and treatment groups is depicted in Figure 12A. As apparent from the results, there is no significant difference in terms of bacterial count (Figure 12B) and health between the two groups. Figures 12C and 12D show similar plots, but which exclude data for animals with bacterial counts $>10^4$.

Table 22

AnimalNo	CageNo	Time.ED	Status.dead	Treatment	HealthStatus.24am	logBacCounts

8120	38.1	84	1	C	1	4.079181246
8121	38.1	168	1	C	1	2
8124	38.1	168	0	C	1	2
8125	38.2	168	0	C	1	2
8127	38.2	48	1	C	2	4.544068044
8128	38.2	168	0	C	1	2
8129	38.2	168	0	C	1	3.301029996
8130	38.3	96	1	T	1	2
8131	38.3	168	0	T	2	3.477121255
8132	38.3	84	1	T	1	2
8133	38.3	168	0	T	1	2
8134	38.3	150	1	T	2	2.77815125
8135	38.4	84	1	C	1	2
8136	38.4	54	1	C	2	4.397940009
8137	38.4	54	1	C	2	3.255272505
8138	38.4	54	1	C	2	3.643452676
8139	38.4	168	0	C	1	2
8140	38.5	132	1	T	2	2
8141	38.5	84	1	T	2	2
8142	38.5	48	1	T	2.5	3.84509804
8143	38.5	168	0	T	1	2
8144	38.6	84	1	C	1	2
8145	38.6	84	1	C	1	2
8146	38.6	48	1	C	2	4.301029996
8147	38.6	168	0	C	1	2
8148	38.6	132	1	C	1	2
8149	38.7	168	0	T	1	2
8150	38.7	168	0	T	1	2
8151	38.7	168	0	T	1	2
8152	38.7	168	0	T	1	2
8153	38.7	168	0	T	1	2
8154	38.8	168	0	C	1	2
8155	38.8	84	1	C	1	2
8156	38.8	48	1	C	3	5
8157	38.8	48	1	C	2	4.740362689
8159	38.9	168	0	T	1	2
8160	38.9	54	1	T	3	4.477121255
8162	38.9	168	0	T	1	2
8163	38.9	168	0	T	2	2
8164	38.1	78	1	T	1	2
8166	38.1	72	1	T	1	2
8167	38.1	168	0	T	1	2
8168	38.11	168	0	C	1	2
8169	38.11	168	0	C	1	2
8170	38.11	78	1	C	1	2

Experiment B: Using the procedure described above, 60 mice were pouched, irradiated (495 rads) and infected (0.2 ml of 0.1 OD 600). The animals were randomly assigned to control and treatment groups. Controls received 250 μg/mouse of isotype control and treated received 250 μg/mouse of anti-VEGF antibody. At 24h, 10 of the 30 animals (sickest animals) in each group were bled and injected with the appropriate solution containing ceftriaxone (Group 1). The remaining 20 animals per group were injected with the antibodies, but without ceftriaxone (Group 2). At 48 hours, Group 1 animals received antibody and no ceftriaxone, while Group 2 animals were bled and received antibody and ceftriaxone. All animals were injected with antibodies daily for a total of 5 days. Blood was used to determine bacterial counts and to prepare plasma. Plasma aliquots were stored at –

80C. The results are provided in Table 23 and are depicted in Figures 13A-13D. Results obtained from animals that received ceftriaxone at 48 hours are shown. The survival difference between the control and treatment groups is depicted in Figure 13A. There is no significant difference in terms of bacterial count (Figure 13B) and health between the two groups. Figures 13C and 13D show similar plots, but which exclude animals with bacterial counts $>10^4$.

Table 23

AnimalNo	CageNo	Time.ED	Status.dead	logBacCounts	Treatment	HealthStatus.24am	Cef
8195	40.1	78	1	1.51851394	C	2	24
8196	40.1	54	1	1.819543936	C	1	24
8197	40.1	168	0	1.51851394	C	1	24
8198	40.1	168	0	1.51851394	C	1	24
8199	40.1	162	1	1.51851394	C	1	24
X33	40.2	168	0	1.51851394	T	1	48
X34	40.2	168	0	1.51851394	T	1	48
X35	40.2	162	1	2	T	2	24
X36	40.2	54	1	3.544068044	T	2	24
X37	40.2	168	0	1.51851394	T	1	48
X38	40.3	132	1	1.51851394	C	1	48
X39	40.3	54	1	3.84509804	C	2	24
X40	40.3	108	1	1.51851394	C	2	24
X41	40.3	60	1	4.568201724	C	1	48
X42	40.3	66	1	4.903089987	C	1	48
X43	40.4	66	1	2	T	2	24
X44	40.4	168	0	1.51851394	T	1	24
X45	40.4	108	1	2	T	1	24
X46	40.4	168	0	1.819543936	T	1	24
X47	40.4	90	1	1.51851394	T	1	24
X48	40.5	168	0	1.51851394	C	1	48
X49	40.5	138	1	3.903089987	C	2	24
X50	40.5	114	1	3.079181246	C	1	48
X51	40.5	168	0	1.51851394	C	1	48
X52	40.5	48	1	5.176091259	C	2	24
X53	40.6	60	1	5.698970004	T	1	48
X54	40.6	168	0	1.51851394	T	1	48
X55	40.6	168	0	1.51851394	T	1	48
X56	40.6	54	1	3.568201724	T	2	24
X57	40.6	138	1	1.51851394	T	1	48
X58	40.7	54	1	4.012837225	C	2	24
X59	40.7	168	0	1.51851394	C	1	48
X60	40.7	132	1	1.51851394	C	1	48
X61	40.7	168	0	1.51851394	C	1	48
X62	40.7	114	1	1.51851394	C	1	48
X63	40.8	60	1	6.77815125	T	1	48
X64	40.8	168	0	1.51851394	T	1	48
X66	40.8	84	1	2.698970004	T	2	24
X67	40.8	60	1	4.84509804	T	1	48
X68	40.9	66	1	4.698970004	C	1	48
X69	40.9	166	1	1.51851394	C	1	48
X70	40.9	48	1		C	1	dead.48
X71	40.9	168	0	1.51851394	C	1	48
X72	40.9	54	1	6	C	1	48
X73	40.1	168	0	2.84509804	T	1	48
X74	40.1	168	0	1.51851394	T	1	48
X75	40.1	60	1	4.77815125	T	1	48
X76	40.1	108	1	2	T	1	48
X77	40.1	166	1	1.51851394	T	1	48
X78	40.11	162	1	1.51851394	C	1	48
X79	40.11	60	1	5.301029996	C	1	48
X80	40.11	60	1	5.602059991	C	1	48
X81	40.11	48	1		C	1	dead.48
X83	40.12	132	1	4.230448921	T	1	48
X84	40.12	168	0	2.477121255	T	1	48

X85	40.12	168	0	1.51851394	T	1	48
X86	40.12	168	0	1.51851394	T	1	48
X90	40.13	66	1	3.579783597	T	1	48
X91	40.13	168	0	2.84509804	T	1	48
X92	40.13	48	1	5	T	2	24

Figures14A-14D shows plots of the combined data for animals that received ceftriaxone from experiments A and B above. The survival difference between the combined control and treatment groups is depicted in Figure 14A. There is no difference in terms of bacterial count (Figure 14B) and health between the two groups. Figures 14C and 14D show similar plots, but which exclude animals with bacterial counts >10^4.

Figures 15A-15D shows plots of the combined data for all animals used in experiments A and B above. The survival difference between the combined control and treatment groups is depicted in Figure 15A. There is no difference in terms of bacterial count (Figure 15B) and health between the two groups. Figures 15C and 15D show similar plots, but which exclude data for animals with bacterial counts >10^4.

Experiment C: Using the procedure described above, 32 mice were pouched, irradiated (495 rads) and infected (0.2 ml of 0.1 OD 600). The animals were randomly assigned to control and treatment groups. Four hours after infection, controls received 250 µg/mouse of isotype control and treated received 250 µg/mouse of anti-VEGF antibody. At 24h after infection animals were bled. At 30h after infections all animals were injected with saline. At 48h after infection animals were injected with the respective antibody solutions containing ceftriaxone at a concentration to yield 0.1mg/mouse. At 53h animals were bled. Blood was used to determine bacterial counts and to prepare plasma. Plasma aliquots were stored at –80C. The results are provided in Table 24 and are graphically represented in Figures 16A-16D. In particular, the survival difference between the control and treatment groups is depicted in Figure 16A. There is no difference in terms of bacterial count (Figure 16B) and health between the two groups. Figures 16C and 16D show similar plots, but which exclude animals with bacterial counts >10^4.

Table 24

AnimalNo	CageNo	Infection	Time.dead	Status.dead	Treatment	Score.d1.am	cumWL.d1	logBacCount.d1
1526	1	YES	54	1	isotype	1	-4.608294931	2
1527	1	YES	138	0	aVEGF	1	-4.545454545	2
1528	1	YES	54	1	aVEGF	2	-8.095238095	4.477121255
1529	1	YES	62	1	isotype	2	-7.881773399	2.477121255
1530	1	YES	54	1	isotype	2	-2.34741784	2
1531	2	YES	138	0	aVEGF	1	-8.212560386	2
1532	2	YES	84	1	isotype	1	-5.11627907	2.301029996
1533	2	YES	48	1	aVEGF	2	-10.05025126	4.176091259

1534	2	YES	138	1	isotype	2	-6.060606061	2
1535	2	YES	62	1	isotype	1	-4.245283019	2
1536	3	YES	36	1	aVEGF	3.5	-12.44019139	5.301029996
1537	3	YES	54	1	isotype	2	-10.95238095	3.51851394
1538	3	YES	138	0	aVEGF	1	-4.444444444	2
1539	3	YES	48	1	isotype	2	-8.482142857	4
1540	3	YES	108	1	aVEGF	1	-8.298755187	2.477121255
1541	4	YES	138	0	aVEGF	1.5	-4.07239819	2
1542	4	YES	138	0	isotype	1	-4.285714286	2
1543	4	YES	62	1	isotype	2	-8.878504673	2.77815125
1544	4	YES	62	1	aVEGF	1.5	-8.095238095	2.477121255
1545	4	YES	138	0	aVEGF	1.5	-3.619909502	2
1546	5	YES	138	0	isotype	1.5	-4.845814978	2
1547	5	YES	138	0	aVEGF	1	-3.720930233	2
1548	5	YES	138	0	isotype	1	-4.147465438	2
1549	5	YES	54	1	aVEGF	1	-9.589041096	3.301029996
1550	5	YES	138	0	aVEGF	1	-4.464285714	2.903089987
1651	6	YES	138	0	aVEGF	1.5	-6.666666667	2
1652	6	YES	138	1	isotype	1	-1.435406699	2
1653	6	YES	138	0	aVEGF	1.5	-2.764976959	2
1654	6	YES	36	1	isotype	2.5	-7.373271889	5.477121255
1655	6	YES	48	1	isotype	2	-8.035714286	4.301029996
1656	7	YES	54	1	aVEGF	2	-9.76744186	3.531478917
1657	7	YES	62	1	isotype	1	-2.314814815	2

Experiment D: Using the procedure described above, 40 mice were pouched, irradiated (495 rads) and infected (0.2 ml of 0.1 OD 600). The animals were randomly assigned to control and treatment groups. Twelve hours after infection, controls received 250 μg/mouse of isotype control and treated received 250 μg/mouse of anti-VEGF antibody. At 24h after infection, animals were bled. At 36h after infection, animals were injected with the respective antibody solutions containing ceftriaxone at a concentration to yield 0.1mg/mouse. Blood was used to determine bacterial counts and to prepare plasma. Plasma aliquots were stored at –80C. The results are provided in Table 25 and are graphically represented in Figures 17A-17D. The survival difference between the control and treatment groups is depicted in Figure 17A. There is no significant difference in terms of bacterial count (Figure 17B) and health between the two groups. Figures 17C and 17D show similar plots, but which exclude animals with bacterial counts $>10^4$.

Table 25

Treatment2	Time.dead	Status.dead	logBacCount.d1	HealthScore.d1.10am
aVEGF	168	0	2.73E+00	a
aVEGF	168	0	1.52E+00	a
aVEGF	144	1	3.22E+00	a
aVEGF	168	0	1.52E+00	a
aVEGF	58	1	4.79E+00	b
aVEGF	144	1	1.52E+00	a
aVEGF	168	0	1.52E+00	a

aVEGF	78	1	2.12E+00	a
aVEGF	52	1	5.02E+00	b-c
aVEGF	52	1	4.08E+00	b
aVEGF	168	0	1.52E+00	a
aVEGF	168	0	2.37E+00	a
aVEGF	150	1	1.52E+00	a
aVEGF	168	0	1.52E+00	a
aVEGF	52	1	4.88E+00	b-c
aVEGF	168	0	1.52E+00	a
isotype	41	1	4.27E+00	b
isotype	41	1	4.88E+00	b
isotype	168	0	1.52E+00	a
isotype	168	0	2.12E+00	a-b
isotype	168	0	1.52E+00	a
isotype	58	1	4.29E+00	b
isotype	168	0	1.52E+00	a
isotype	120	1	1.52E+00	b
isotype	168	0	1.52E+00	a
isotype	78	1	3.43E+00	b
isotype	84	1	2.00E+00	a
isotype	58	1	4.70E+00	b
isotype	102	1	3.12E+00	b
isotype	52	1	4.40E+00	b
isotype	58	1	2.90E+00	a
isotype	58	1	2.70E+00	b

Figures18A-18D depict plots of the combined data for animals that received anti-VEGF antibody or VEGF isotype control antibody treatment from Experiments C and D. The survival difference between the combined control and treatment groups is depicted in Figure 18A. There is no significant difference in terms of bacterial count (Figure 18B) and health between the two groups. Figures 18C and 18D show similar plots, but which exclude animals with bacterial counts $>10^4$. Figures 19A-19B shows plots of the combined data for all animals used in experiments A and B above, but with the survival time considered to have started at the time of treatment rather than the time of infection.

Treatment with anti-JE (MCP-1) antibody:

Previous experiments showed that treating septic animals with an anti-VEGF antibody improved their survival as compared to an untreated group. Similar to VEGF, experiments were conducted with anti-JE antibody, and JE (murine MCP-1) levels were found to be elevated in doomed, immunocompromised animals as compared to those animals that survived (Figure 20).

The antibody was prepared as follows. Twenty-week old Sprague Dawley rats were immunized subcutaneously with rMuMCP-1 (R&D Systems, Inc. Cat# 479-JE/CFz). Each rat was injected with a 0.5mL combination of rMuMCP-1, Benadryl (Sigma), and Freund's Adjuvant (Sigma) divided between 2 injection sites given intradermally (ID) and intraperitoneally (IP). The prescribed immunization protocol was for each rat to receive a total of 9 injections over a 9-month timeframe. The first and second injections consisted of 50 μg rMuMCP-1 in 250 μL PBS + 36 μL Benadryl emulsified with an equal volume of Complete Freund's adjuvant. For the rest of the injections, each rat received 50μg rMuMCP-1 + Benadryl as before with the exception of Incomplete Freund's Adjuvant (see De St. Groth, F, S and D Scheidegger, Production of Monoclonal Antibody: Strategy and Tactics. Journal of Immunological Methods 35:1-21, 1980). The rats were bled at various time-points throughout the immunization schedule. Blood collections were performed by retro-orbital puncture and serum was collected, frozen, and shipped on dry ice for titer determination by solid phase EIA. Seven days following the 9th injection, rats C73 and C74 were given a final IV booster injection of 10 μg rMuMCP-1 diluted in 120 μL PBS. Three days later the rats were euthanized by $C0_2$ asphyxiation, and the spleens aseptically removed and immersed in 10 mL cold PBS/PSA (PBS containing PSA which is 100 U/ml penicillin, 100 μg/ml streptomycin, and 0.25 μg/ml amphotericin B). The splenocytes were harvested by sterilely perfusing the spleen with cold perfusion medium (DMEM, 20% FBS, 1 mM sodium pyruvate, 4 mM L-glutamine, 1% MEM nonessential amino acids, and 1% Origen (IGEN)). The cells were enumerated on a Coulter counter, washed once, and resuspended in 10mL perfusion medium.

The non-secreting mouse myeloma fusion partner, P3 x 63 Ag 8.653 (653), cell line was expanded in RPMI 1640 medium (JRH Biosciences) supplemented with 10% (v/v) FBS (Cell Culture Labs), 1 mM sodium pyruvate, 0.1 mM NEAA, 2 mM L-glutamine (all from JRH Biosciences) and cryopreserved in 95% FBS and 5% DMSO (Sigma), then stored in a

vapor phase liquid nitrogen freezer. The cell bank was sterile and free of mycoplasma (Bionique Laboratories).

A cell bank of the non-secreting Balb/c mouse myeloma fusion partner FO was purchased from ATCC (# CRL-1646). One frozen vial of FO cells was thawed and resuspended in αMEM (modified) medium (JRH Biosciences) supplemented with 10% (v/v) FBS (Cell Culture Labs), 1 mM sodium pyruvate, 0.1 mM NEAA, 2 mM L-glutamine (all from JRH Biosciences). The cells were expanded, cryopreserved in 95% FBS and 5% DMSO (Sigma) and stored in a vapor phase liquid nitrogen freezer. The cell bank was sterile and free of mycoplasma (Bionique Laboratories).

Prior to fusion, myeloma cells were thawed and maintained at log phase in the media described above. On fusion day, the cells were washed in PBS, counted, and viability determined (>95%) via trypan blue dye exclusion.

Fusion was carried out at a 1:1 ratio of FO or 653 murine myeloma cells to viable spleen cells (Rat#C73 with FO, Rat#C74 with 653). Spleen and myeloma cells were mixed together and pelleted. The pellet was resuspended with 5 mL of 50%(w/v) PEG/PBS solution (using PEG molecular weight 1450 for rat #C74 fusion and PEG molecular weight 3000 for rat #C73) at 37^0C. Cell fusion was allowed to occur for 2 minutes at 37^0C. The fusion was stopped by slowly adding 25 mL DMEM (no additives) at 37^0C. Fused cells were centrifuged for 5 minutes at 1000 rpm, drawn up into 25 mL pipette, and expelled into a 225cm^2 flask (Costar, 431082) containing 240 mL of Fusion Medium (DMEM, 20% FBS, 1 mM sodium pyruvate, 4 mM L-glutamine, 1% MEM nonessential amino acids, 1% Origen, 25 μg/ml gentamicin, 100 μM hypoxanthine, 0.4 μM aminopterin, and 16 μM thymidine). The cells were allowed to sit for 4 hours at 37^0C, an additional 360 mL of 37^0C Fusion Medium was added to the flask, the flask was swirled to resuspend the cells. The cells were then seeded at 200 μL/well in thirty 96-well flat bottom tissue culture plates (Costar, 3595) per fusion. The fusion plates were placed in a humidified 37^0C incubator at 5% CO_2 for 7-10 days. The media was changed by taking off 100 μl medium adding 100 μl HT medium after 7 days (5, 6).

Solid phase EIA was used to screen rat sera for antibodies specific for rMuMCP-1. Briefly, plates (Costar, 9018) were coated with rMuMCP-1 at 1 μg/mL in PBS, pH 7.4 on to 96-well EIA plates (Nunc) and incubated overnight at 4°C. The plates were then washed three times in 0.15 M saline with 0.02% v/v Tween 20, the wells were then blocked with 1%

(w/v) BSA (Sigma) in PBS, 200 μL/well for 1 hour at 37°C. Plates were used immediately or frozen at -20°C for future use. The diluted sera were incubated on the rMuMCP-1 coated plates at 50 μL/well at 37°C for 0.5 hour. The plates were washed and then probed with 50 μL/well HRP-labeled goat anti-Rat IgG (Fc) specific antibody (Jackson Immune Research Cat#112-035-071) diluted 1:20,000 in 1% BSA-PBS for 30 minutes at 37°C. The plates were again washed and 100 μL/well of citrate-phosphate substrate solution (0.1M citric acid, 0.2M sodium phosphate, 0.01% H_2O_2, 1 mg/mL OPD (Sigma) was added for approximately 15 minutes at RT. The reaction was stopped by the addition of 25 μL/well, 4N H_2SO_4. The absorbance was measured at 490 nm by an automated plate spectrophotometer.

Hybridomas arising from the fusion of rat lymphocytes with murine myeloma cells were evaluated by EIA for their ability to secrete anti-MuMCP-1 antibodies. Briefly, plates were coated with rMuMCP-1 at 1μg/mL in PBS overnight at 4^0C, washed and blocked as above. Undiluted hybridoma supernatants were incubated on plates for 30 minutes at RT (room temperature). All fusion plates were tested. The plates were washed and then probed with 50 μL/well HRP-labeled goat anti-Rat IgG Fc specific antibody diluted 1:20,000 in 1% BSA-PBS for 30 minutes at 37°C. The plates were washed again and incubated with citrate-phosphate substrate solution as described above. Cells in positive wells were transferred to 24-well plates to increase cell numbers and later subcloned by limiting dilution.

Isotype determination of the antibodies was accomplished by use of Rat MonoAB ID/SP kit (Zymed Cat#93-9550) in EIA format. Plates were coated at 50 μL/well overnight at 4^0C with rMuMCP-1 at 1 μg/ml in PBS, washed, and blocked as above. Spent supernatant from each Mab applied to 96-well plate at 50 μL/well. The plates were incubated at 37^0C for 30 minutes and then washed. Next, one drop of biotinylated antibody control or subclass specific biotinylated anti-rat immunoglobulin was added to each column, incubated at 37^0C for 30 minutes, and washed. Diluted HRP-Streptavidin {one drop concentrated conjugate/2.5ml PBS-Tween (50mM PBS + one drop of 50%Tween20 for every 50 ml buffer)} was added to all the wells and incubated at 37^0C for 30 minutes. Plates were again washed then incubated for 15 minutes at RT with 50 μL/well of citrate-phosphate substrate solution (0.1M citric acid and 0.2M sodium phosphate, 0.01% H_2O_2, and 1 mg/mL OPD). Substrate development was stopped by addition of 4N sulfuric acid at 50μL/well and the absorbance was measured at 490nm via an automated plate spectrophotometer.

During the time-course experiment, the increase in JE/MCP-1 levels from time 0 to 4 hours and time 0 to 10 hours after infection was higher in irradiated and infected animals (doomed) as compared to non-irradiated and infected animals (survivors). Also similar to VEGF, JE/MCP-1 has the ability to induce angiogenesis and vascular permeability. Finally, VEGF is known to induce JE/MCP-1 expression. Therefore, two experiments were performed to determine if neutralization of JE/MCP-1 improves survival of septic animals.

Experiment A: Using the procedure described above, 76 mice were pouched, irradiated (495 rads) and infected (0.2 ml of 0.1 OD 600). Sixteen hours after infection, animals were separated into treatment groups according to a computer-generated random sequence and were injected with 0.4 ml of PBS (Groups A and C) or 0.4 ml of an anti-MCP1/JE antibody (400 μg/mouse) in PBS (Group B). After 24 hours (40 hours post-infection), each animal was bled (150 μl/mouse in a capillary tube containing 20 μl EDTA) and injected as follows: Group A, 0.4 ml isotype control (450 μg/mouse in PBS); Group B, 0.4 ml PBS; and Group C, 0.4 ml of PBS containing 450 μg/mouse of anti-MCP1/JE. At 40 h after injection, all injections contained ceftriaxone to yield a dose of 100 μg/mouse. Blood was used to determine bacterial counts and to prepare plasma. Two aliquots of 20 μl and an extra aliquot were prepared and stored at –80°C. The results are provided in Table 26 and are graphically represented in Figures 21A-21X. Figures 21A-21H show plots of data from all animals used in experiment A. The survival differences among groups A, B, and C are depicted in Figure 21A. The survival difference between groups A and C is depicted in Figure 21B. The survival difference between groups A and B is depicted in Figure 21C. The survival difference between groups B and C is depicted in Figure 21D. There is no significant difference in terms of bacterial count and health between the three groups, as seen in Figures 21E-21H. Figures 21I-21L show plots of data from animals used in experiment A that had bacterial counts $<10^4$. The survival differences among groups A, B, and C are

depicted in Figure 21I. The survival difference between groups A and C is depicted in Figure 21J. The survival difference between groups A and B is depicted in Figure 21K. The survival difference between groups B and C is depicted in Figure 21L. There is no significant difference in terms of bacterial count and health between the three groups, as seen in Figures 21M-21P. Figures 21Q-21X show plots of data from animals used in experiment A that did not die and were not euthanized before the second treatment. The survival differences among groups A, B, and C are depicted in Figure 21Q. The survival difference between groups A and C is depicted in Figure 21R. The survival difference between groups A and B is depicted in Figure 21S. The survival difference between groups B and C is depicted in Figure 21T. There is no significant difference in terms of bacterial count and health between the three groups, as seen in Figures 21U-21X.

Table 26

CageNo	AnimalNo	Bad	Treat1	Treat2	logBC	status	time	status.dead
1	380	0	anti-JE	PBS	5.778151	FD	47	1
1	381	0	anti-JE	PBS	2	LIVE	166	0
1	498	0	PBS	anti-JE	2.30103	LIVE	166	0
1	499	0	PBS	anti-JE	2	LIVE	166	0
1	500	0	PBS	anti-JE	2.60206	LIVE	166	0
2	382	0	PBS	ISO	3.763428	FD	88	1
2	383	0	PBS	ISO	2.30103	LIVE	166	0
2	384	0	PBS	ISO	5.30103	EU	60	1
2	385	0	PBS	anti-JE	2	LIVE	166	0
2	386	0	PBS	anti-JE	2	EU	125	1
3	387	0	PBS	ISO	2	LIVE	166	0
3	388	0	PBS	ISO	2	FD	119	1
3	389	0	anti-JE	PBS	6.30103	FD	47	1
3	390	0	anti-JE	PBS	2	LIVE	166	0
3	391	0	anti-JE	PBS	2	LIVE	166	0
4	392	0	PBS	ISO	2	LIVE	166	0
4	393	1	PBS	ISO	2	LIVE	166	0
4	394	0	PBS	ISO	2	LIVE	166	0
4	395	0	PBS	anti-JE	2	EU	125	1
4	396	0	PBS	anti-JE	2.778151	LIVE	166	0
5	397	0	anti-JE	PBS	2	LIVE	166	0
5	398	0	anti-JE	PBS	2	LIVE	166	0
5	399	0	anti-JE	PBS	4	LIVE	166	0
5	400	0	PBS	anti-JE	4.30103	EU	53	1
5	402	0	PBS	anti-JE	4.30103	EU	101	1
6	404	0	PBS	ISO	3.653213	FD	112	1
6	406	0	PBS	ISO	2.477121	LIVE	166	0
6	407	0	PBS	anti-JE	2	EU	101	1
6	408	0	PBS	anti-JE	6.477121	EU	46	1
6	410	0	PBS	anti-JE	2	EU	149	1
7	411	1	anti-JE	PBS	3.812913	EU	101	1
7	412	0	anti-JE	PBS	5.69897	EU	46	1
7	413	0	anti-JE	PBS	4.477121	EU	53	1
7	414	0	PBS	anti-JE	5.60206	EU	46	1
7	415	0	PBS	anti-JE	5.477121	EU	46	1
8	416	0	anti-JE	PBS	2	ED	166	1
8	417	0	anti-JE	PBS	2.30103	FD	136	1
8	418	0	anti-JE	PBS	2	LIVE	166	0
8	419	0	anti-JE	PBS	2	LIVE	166	0

8	423	0	anti-JE	PBS	2	LIVE	166	0
9	421	0	PBS	ISO	2.778151	LIVE	166	0
9	422	0	PBS	ISO	5.30103	FD	47	1
9	420	1	PBS	PBS	5.30103	EU	53	1
9	424	1	PBS	PBS	2	LIVE	166	0
9	425	1	PBS	PBS	5.30103	EU	53	1
10	426	0	PBS	ISO	4.69897	FD	88	1
10	427	0	PBS	ISO	4.60206	EU	60	1
10	428	0	anti-JE	PBS	6.477121	EU	46	1
10	429	0	anti-JE	PBS		FD	40	1
10	430	0	anti-JE	PBS	6.69897	EU	46	1
11	431	0	PBS	ISO	5.778151	FD	47	1
11	432	0	PBS	ISO	2	FD	119	1
11	433	0	PBS	anti-JE	4	EU	60	1
11	434	0	PBS	anti-JE	2	LIVE	166	0
11	435	0	PBS	anti-JE	2	EU	125	1
12	436	0	PBS	ISO	6.30103	EU	46	1
12	437	0	PBS	ISO	6.477121	EU	46	1
12	438	0	PBS	ISO	4.146128	EU	46	1
12	439	0	PBS	anti-JE	2	LIVE	166	0
12	440	0	PBS	anti-JE	2.69897	LIVE	166	0
13	441	0	anti-JE	PBS	2	LIVE	166	0
13	442	0	anti-JE	PBS	2.60206	LIVE	166	0
13	443	0	PBS	anti-JE	5	EU	60	1
13	444	0	PBS	anti-JE	2	LIVE	166	0
13	445	0	PBS	anti-JE	2	LIVE	166	0
14	446	0	PBS	ISO	2	LIVE	166	0
14	447	0	PBS	ISO	2.778151	FD	47	1
14	448	0	PBS	ISO	2.845098	EU	94	1
14	449	1	anti-JE	anti-JE	2	LIVE	166	0
14	405	1	anti-JE	anti-JE	2.30103	EU	149	1
15	450	0	PBS	anti-JE	2	LIVE	166	0
15	451	0	PBS	anti-JE	5.30103	EU	46	1
15	403	0	PBS	anti-JE	2.845098	FD	136	1
15	474	0	anti-JE	PBS	6.30103	EU	46	1
15	475	0	anti-JE	PBS	2	LIVE	166	0
16		0	PBS	ISO		EU	46	1

Experiment B: Using the procedure described above, eighty mice were pouched, irradiated (495 rads), and infected (0.2 ml of 0.1 OD 600 equivalent to 4-5x10^6CFU/mouse). Sixteen hours after infection, animals were separated into treatment groups according to a computer-generated random sequence and injected: for Group A, with 0.4 ml isotype as a control (450 μg/mouse in PBS); and for Group B, with 0.4 ml of PBS containing 450 μg/mouse of anti-MCP1/JE. After 24 hours (40 hours after infection), each animal was bled (150 μl/mouse in a capillary tube containing 20 μl EDTA) and injected with ceftriaxone (100 μg/mouse). Blood was used for determining bacterial counts and preparing plasma. Two aliquots of 20 μl of plasma and an extra aliquot were prepared and stored at -80°C. At 72-80 hours, some sick (c-d) animals were euthanized and bled. At 96 hours, mice that had no counts at 40 hours were euthanized as controls. At 96 hours, all animals were injected with ceftriaxone (100 μg/mouse). Seven animals were eliminated because they either had a failed

pouch or were injected with the wrong solution at 16 hours. The data are provided in Table 27 and are depicted in Figures 22A-22H. Figures 22A-22F show plots of data from all animals used in Experiment B. The survival difference between groups A and B is depicted in Figure 22A. There are no significant differences in terms of bacterial count and health among the three groups, as seen in Figure 22B. The survival difference between groups A and B, excluding animals with bacterial counts >10^4, is depicted in Figure 22C. There are no significant differences in terms of bacterial count and health among the three groups, as seen in Figure 22D. The survival difference between groups A and B, excluding animals that were euthanized before ceftriaxone treatment, is depicted in Figure 22E. There are no significant differences in terms of bacterial count and health among the three groups, as seen in Figure 22F.

Table 27

CangeNo	AnimalNo	Treatment	bacCount	logBacCount	Time.dead	Status.dead	Status	Bad
1	201	ISO	100	2	166	0	ALIVE	0
1	202	ISO	1000	3	166	0	ALIVE	0
1	203	ISO	20000	4.301029996	112	1	FD	0
1	204	ISO	70000	4.84509804	53	1	ED	0
1	205	ISO	3000	3.477121255	166	0	ALIVE	0
2	206	anti-JE	30000	4.477121255	64	1	FD	0
2	207	anti-JE	50000	4.698970004	77	1	EU	0
2	208	anti-JE	50000	4.698970004	64	1	FD	0
2	209	anti-JE	100	2	166	0	ALIVE	0
2	210	anti-JE	2000	3.301029996	77	1	EU	0
3	211	ISO	2100	3.322219295	77	1	EU	0
3	212	ISO	200000	5.301029996	53	1	ED	0
3	213	ISO	50000	4.698970004	64	1	FD	0
3	214	ISO	100	2	166	0	ALIVE	0
3	215	ISO	150000	5.176091259	54	1	FD	0
4	216	anti-JE	20000	4.301029996	77	1	EU	0
4	217	anti-JE	7000	3.84509804	88	1	FD	0
4	218	anti-JE	100	2	166	0	ALIVE	0
4	219	anti-JE	5000	3.698970004	77	1	EU	0
4	220	anti-JE	100000	5	60	1	EU	0
5	221	ISO	6000000	6.77815125	47	1	FD	0
5	222	ISO	40000	4.602059991	60	1	EU	0
5	223	anti-JE	100	2	166	0	ALIVE	0
5	224	anti-JE	100	2	166	0	ALIVE	0
5	225	anti-JE	100	2	166	0	ALIVE	0
6	226	ISO	5600	3.748188027	77	1	EU	0
6	227	ISO	100	2	166	0	ALIVE	0
6	228	ISO	1000	3	160	1	FD	0
6	229	anti-JE			166	0	ALIVE	1
6	230	anti-JE	100	2	166	0	ALIVE	0
7	231	ISO	4000	3.602059991	101	1	EU	0
7	232	ISO	400000	5.602059991	47	1	FD	0
7	233	anti-JE	800	2.903089987	95	1	FD	0
7	234	anti-JE	1000	3	125	1	EU	0
7	235	anti-JE	200000	5.301029996	53	1	FD	0
8	236	ISO	30000	4.477121255	77	1	EU	0
8	237	ISO	400000	5.602059991	47	1	FD	0

8	238	ISO	200000	5.301029996	54	1	FD	0
8	239	anti-JE	10000	4	136	1	FD	0
8	240	anti-JE	100000	5	54	1	FD	0
9	241	anti-JE	100	2	166	0	ALIVE	0
9	242	anti-JE	130000	5.113943352	60	1	EU	0
9	243	ISO	400000	5.602059991	47	1	FD	0
9	244	ISO	5000	3.698970004	60	1	EU	0
9	245	ISO	100	2	166	0	ALIVE	0
10	246	anti-JE	20000	4.301029996	60	1	EU	0
10	247	anti-JE	100	2	166	0	ALIVE	0
10	248	anti-JE	100	2	166	0	ALIVE	0
10	249	ISO	700	2.84509804	166	0	ALIVE	0
10	250	ISO	5000	3.698970004	112	1	FD	0
11	251	anti-JE	100	2	166	0	ALIVE	0
11	252	anti-JE	100	2	166	0	ALIVE	0
11	253	ISO	10000	4	70	1	ED	0
11	254	ISO	400	2.602059991	166	0	ALIVE	0
11	255	ISO	4400	3.643452676	160	1	FD	0
12	256	anti-JE	100	2	166	0	ALIVE	0
12	257	anti-JE	100	2	166	0	ALIVE	0
12	258	anti-JE	5000	3.698970004	95	1	FD	0
12	259	ISO	10000	4	101	1	EU	0
12	260	ISO	200000	5.301029996	54	1	FD	0
13	261	anti-JE	100	2	166	0	ALIVE	0
13	262	anti-JE	100	2	166	0	ALIVE	0
13	263	ISO	1500	3.176091259	101	1	EU	0
13	264	ISO	2000000	6.301029996	46	1	EU	0
13	265	ISO			166	0	ALIVE	1
14	266	anti-JE	100	2	166	0	ALIVE	0
14	267	anti-JE	100	2	166	0	ALIVE	0
14	268	anti-JE	10000	4	77	1	EU	0
14	269	ISO	20000	4.301029996	101	1	EU	0
14	270	ISO	100	2	166	0	ALIVE	0
15	271	ISO	2000000	6.301029996	46	1	EU	0
15	272	ISO	150000	5.176091259	46	1	EU	0
15	273	anti-JE	300	2.477121255	125	1	EU	0
15	274	anti-JE	100	2	166	0	ALIVE	0
15	275	anti-JE	300000	5.477121255	46	1	EU	0
16	276	ISO	5000	3.698970004	77	1	EU	0
16	277	ISO	100	2	166	0	ALIVE	0
16	278	ISO	30000	4.477121255	70	1	EU	0
16	279	anti-JE	1100	3.041392685	101	1	EU	0
16	280	anti-JE	100	2	166	0	ALIVE	0

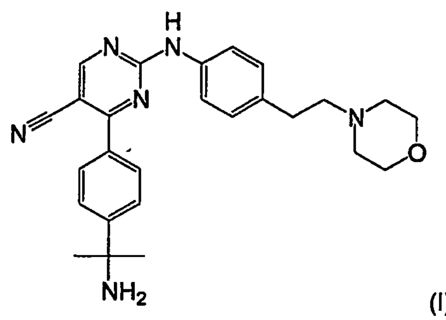
The survival difference between the combined control and treatment groups used in experiments A and B above is depicted in Figure 23A. There is no significant difference in terms of bacterial count (Figure 23B) and health between the two groups. Figures 23C and 23D show similar plots, but which exclude animals with bacterial counts $>10^4$. Figures 23E-23F show plots of the combined data for all animals used in experiments A and B, but which exclude animals that died or were euthanized before the second treatment.

<u>Treatment with VEGF receptor antagonists</u>:

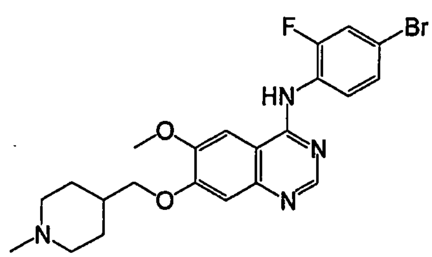
VEGF is known to be a potent vascular permeability factor, inducing adema, hypotension via induction of iNOS, which results in the production of nitrous oxide (NO),

and poor tissue perfusion. VEGF was also found to be elevated in doomed immunocompromised animals (Figure 11). Additionally, the experiments described above showed that treating septic animals with an anti-VEGF antibody improved their survival as compared to an untreated group. The following experiment was performed in order to determine the effects of treating animals with test VEGF antagonists.

Using the procedure described above, 76 mice were pouched, irradiated (495 rads) and infected (0.2 ml of 0.1 OD 600). Sixteen hours later, animals were injected with 0.2ml of diluent, Compound I or Compound II (100mg/Kg), which have the following structures:



(I) (see U.S. Patent No. 6,579,983);



(II) (see WO 98/13354 and WO 00/132651).

At 40 hours after infection, animals were bled and injected with the same solutions to which ceftriaxone was added to yield a solution containing 50ug/mouse. Animals were injected with the solutions (no ceftriaxone) for 2 more days. Blood was used for BC and plasma. Two aliquots of 20ul and an extra aliquot were prepared and stored at -80. Table 28 reports the bacterial counts and the time of euthanasia.

Table 28

Treatment	Bacterial counts	Time of Death	Status

Control	FD	40	1
Control	FD	40	1
Control	2.0E+06	48	1
Control	1.0E+06	48	1
Control	9.0E+05	48	1
Control	3.0E+05	64	1
Control	2.0E+05	70	1
Control	1.5E+05	48	1
Control	7.0E+04	70	1
Control	6.0E+04	54	1
Control	3.5E+04	48	1
Control	7.0E+03	72	1
Control	4.6E+03	78	1
Control	1.0E+03	112	1
Control	2.0E+02	168	0
Control	2.0E+02	160	1
Control	<100	168	0
Control	<100	72	1
Control	<100	112	1
Control	<100	168	0
Control	<100	112	1
Control	<100	112	1
Control	<100	160	1
Control	<100	168	0
Control	<100	168	0
Compound I	FD	40	1
Compound I	FD	40	1
Compound I	FD	40	1
Compound I	1.3E+07	46	1
Compound I	4.0E+06	46	1
Compound I	3.0E+06	46	1
Compound I	2.0E+06	46	1
Compound I	1.0E+06	48	1

Compound I	3.0E+05	64	1
Compound I	3.0E+05	48	1
Compound I	3.0E+05	48	1
Compound I	2.0E+05	46	1
Compound I	2.0E+05	48	1
Compound I	3.0E+04	88	1
Compound I	1.7E+03	94	1
Compound I	1.0E+03	112	1
Compound I	1.0E+02	112	1
Compound I	1.0E+02	160	1
Compound I	1.0E+02	96	1
Compound I	1.0E+02	112	1
Compound I	1.0E+02	112	1
Compound I	<100	96	1
Compound I	<100	112	1
Compound I	<100	112	1
Compound I	<100	112	1
Compound I	<100	112	1
Compound I	<100	96	1
Compound I	<100	168	0
Compound II	FD	40	1
Compound II	FD	40	1
Compound II	1.0E+09	46	1
Compound II	1.0E+07	46	1
Compound II	9.0E+06	48	1
Compound II	3.0E+06	46	1
Compound II	2.0E+06	48	1
Compound II	2.0E+06	48	1
Compound II	2.0E+06	64	1
Compound II	5.0E+05	48	1
Compound II	3.0E+05	48	1
Compound II	3.0E+05	46	1
Compound II	5.0E+04	64	1
Compound II	3.0E+04	64	1

Compound II	1.6E+04	48	1
Compound II	2.0E+03	160	1
Compound II	1.0E+02	112	1
Compound II	1.0E+02	48	1
Compound II	<100	112	1
Compound II	<100	112	1
Compound II	<100	168	0
Compound II	<100	160	1
Compound II	<100	160	1
Compound II	<100	168	0
Compound II	<100	168	0
Compound II	<100	168	0
Compound II	<100	64	1

Figures 25A-25B show the survival curves. While no statistically significant survival difference was observed, a survival advantage was noted for animals with less than 10e5 bacterial counts as compared to the control. This survival advantage is noted from the hours from 48 to 88. During this period, 6 out of 17 animals died in the control group, while zero out of 15 animals died in the treatment group.

Treatment with a PPARγ agonist:

It is known that treatment with rosiglitazone improves survival in animal models of CLP sepsis. Rosiglitazone is also an antidiabetic drug, and diabetes is a known risk condition for sepsis and septic shock. The efficacy of rosiglitazone in treating sepsis was therefore modeled as follows.

Sixty-one mice were pouched, irradiated, and infected in the manner described above. Sixteen hours post-infection, 20 mice were injected with a 0.2 ml rosiglitazone solution to a final concentration of 50 μg/mouse, 20 mice were injected with a 0.2 ml rosiglitazone solution to a final concentration of 200 μg/mouse, and 21 mice were injected with 0.2 ml of diluent alone. At 40 and 92 hours post-infection, each group of mice were injected with the same solution that they were injected with at forty hours post-infection, to which was added ceftriaxone to deliver 100 μg/mouse. Figure 26 shows the survival rates for the three groups of animals, which indicate that both the 50 μg/ml and the 200 μg/ml rosigliazone treatments each confers a significant survival advantage compared to the treatment with diluent alone.

Example 9: Determination of a Biomarker Panel in an Immunocompromised Mouse Model Using a Larger Data Pool

Using the data obtained in Experiments c, d, e and f described in Example 1 and shown in Appendix A together, an additional biomarker panel was identified. Analysis of variance (ANOVA) with each experiment treated as a random block was used to assess each analyte's discrimination power between Doomed and Survived animals. There were 11 analytes having test p values are less than 0.01, and 14 analytes having test p values less than 0.05. The weight for each analyte was defined as the standardized fixed effect size from the above analysis. The score for each animal was defined as the sum of the product of the log 2 value of each analyte's measured level with its corresponding weight over all 7 analytes.

The seven analytes identified were MCP-3, MCP-5, TIMP-1, RANTES, TPO, TNFα, and IL-3. This biomarker panel was successfully used to predict disease outcome in the animal model in a manner similar to that described in Examples 3, 4, and 5. The results from these studies are shown in Appendix B. Accordingly, this group of analytes constitutes a preferred embodiement of a biomarker panel.

Although the invention has been described above by reference to a detailed description of illustrative and preferred features and embodiments, it will be understood that the invention is intended not to be limited by the foregoing, but to be defined by the appended claims as properly construed under principles of patent law.

	A	B	C	D	E	F	G	H	I	J	K	L
1	**APPENDIX A:** This appendix contains all the data obtained by RBM for the samples reported on Tables for experiments c, d, e,											
2	and f. Pool 3 refers to control plasma samples obtained from C3H/HeJ mice hat did not receive any treatment and represent a pool											
3	of samples.											
4			Animal	RBM	ApoA-1	B2M	CRP	D-dimer	EGF	Endothelin-1	Eotaxin	Factor 7
5	Exp.	Description	Number	test date	ug/ml	pg/ml	ug/ml	ng/ml	pg/ml	pg/ml	pg/ml	ng/ml
6	c	CONTROL	2255	NOV	84.9	905		2.36	9.13	31.1	1530	1.62
7	c	CONTROL	2257	NOV	77.3	866		3.43	11.2	39.5	1870	1.11
8	c	CONTROL	2259	NOV	81.1	981		4.66	17.8	29.8	1940	2.14
9	c	CONTROL	2263	NOV	95.2	862		4.38	20.1	46.1	1450	2.36
10	c	CONTROL	2266	NOV	89.8	961		2.76	13.4	39.5	1210	1.58
11	c	CONTROL	2268	NOV	85.4	985		6.03	17.8	41.7	1690	2.4
12	c	CONTROL	2271	NOV	73.2	916		3.03	9.13	24.4	2360	1.33
13	c	CONTROL	2272	NOV	78	780		1.22	3.15	24.4	1500	0.617
14	c	DOOMED	2287	NOV	79.1	981		3.57	20.1	37.2	4120	1.4
15	c	DOOMED	2288	NOV	75.3	3010		11.7	40	41.7	5240	1.91
16	c	DOOMED	2290	NOV	85.9	981		6.03	15.6	43.9	4330	2.1
17	c	FINAL	2287	NOV	63.9	1500		8.49	50.8	70.4	5680	4.44
18	c	FINAL	2290	NOV	55.3	1270		5.21	20.1	41.7	5050	1.84
19	c	INFECTED	2277	NOV	99.8	1050		5.48	21.2	43.9	2950	1.91
20	c	INFECTED	2282	NOV	101	1000		6.31	17.8	43.9	1980	1.8
21	c	INFECTED	2283	NOV	93.8	1190		3.84	16.7	41.7	2730	1.54
22	c	SURVIVED	2286	NOV	81.9	988		3.03	14.5	21.6	2600	1.4
23	c	INFECTED	2278	DEC	91.9	7450		3.04	21.2	46.5	1390	1.9
24	c	INFECTED	2279	DEC	68.7	6730		1.43	14.2	33.3	1270	1.5
25	c	INFECTED	2280	DEC	77.8	7140		1.18	11.3	30.9	909	1.75
26	c	INFECTED	2281	DEC	78.7	6860		2.31	5.68	40.1	1090	1.75
27	c	SURVIVED	2284	DEC	77.2	7370		3.34	21.2	42.3	2050	1.9
28	c	SURVIVED	2285	DEC	81.5	6460		3.1	19.2	44.4	1960	2.19
29	c	SURVIVED	2289	DEC	77.2	7450		1.68	23.2	48.6	3460	2.77
30	d	FINAL	6515	MARCH		785			3.57	31	1700	0.649
31	d	FINAL	6521	MARCH		1490			20.4	31	1700	1.72
32	d	FINAL	6530	MARCH		785			11.3	31	1700	0.313
33	d	FINAL	6531	MARCH		896			14.5	41.8	1700	0.807
34	c	CONTROL	2255	MARCH		209			2.27	90.7	48.3	3.9
35	c	CONTROL	2257	MARCH		350			14.5	96.1	191	2.45
36	c	CONTROL	2259	MARCH		459			7.78	96.1	145	4.38
37	c	CONTROL	2263	MARCH		404			7.78	96.1	70.9	4.38
38	c	CONTROL	2266	MARCH		209			2.27	62.5	16.4	1.57
39	c	CONTROL	2268	MARCH								
40	c	CONTROL	2271	MARCH		567			2.27	79.1	249	3.56
41	c	CONTROL	2272	MARCH		567			2.27	90.7	197	1.87
42	c	DOOMED	2290	MARCH		246			2.27	66	1080	3.15

	A	B	C	D	E	F	G	H	I	J	K	L
43	c	**FINAL**	2287	MARCH								
44	c	**FINAL**	2290	MARCH		3310			44.2	140	**1700**	6.39
45	c	**INFECTED**	2277	MARCH		1130			20.4	123	**1700**	3.97
46	c	**INFECTED**	2282	MARCH		703			14.5	101	1620	3.28
47	c	**INFECTED**	2283	MARCH		1370			14.5	96.1	**1700**	3.42
48	c	**SURVIVED**	2286	MARCH		431			26	101	**1700**	5.08
49	d	**CONTROL**	2260	MARCH		350			3.57	41.8	**1700**	3.01
50	d	**CONTROL**	2261	MARCH		513			11.3	87.9	**1700**	4.52
51	d	**CONTROL**	2262	MARCH		896			17.5	96.1	**1700**	6.53
52	d	**DOOMED**	6514	MARCH		785			2.27	96.1	**1700**	4.66
53	d	**DOOMED**	6526	MARCH		1690			3.57	90.7	**1700**	3.97
54	d	**DOOMED**	6530	MARCH		1340			17.5	101	**1700**	3.56
55	d	**DOOMED**	6534	MARCH		1430			14.5	93.4	**1700**	3.56
56	d	**DOOMED**	6535	MARCH		1620			14.5	85	**1700**	2.45
57	d	**SURVIVED**	6507	MARCH		785			7.78	50.8	**1700**	4.24
58	d	**SURVIVED**	6508	MARCH		513			7.78	90.7	**1700**	3.69
59	d	**SURVIVED**	6512	MARCH		1130			9.59	90.7	**1700**	3.69
60	d	**SURVIVED**	6532	MARCH		1980			21.8	72.8	**1700**	5.22
61	d	**SURVIVED**	6537	MARCH		1040			17.5	96.1	**1700**	3.01
62	d	**DOOMED**	6509	JUNE	107	882	0.407		12.5	28.8	2600	0.349
63	d	**DOOMED**	6509	JUNE	113	1330	0.387		15.9	52.3	2590	0.53
64	d	**DOOMED**	6515	JUNE	128	675	0.606		29.6	28.8	2410	0.964
65	d	**DOOMED**	6515	JUNE	138	397	0.751		26.2	28.8	2480	1.01
66	d	**DOOMED**	6520	JUNE	125	1460	**0.221**		17.6	22.8	2270	1.71
67	d	**DOOMED**	6520	JUNE	126	1340	0.221		3.73	43.7	2200	1.67
68	d	**DOOMED**	6528	JUNE	116	1290	0.429		22.8	**6.07**	3190	0.964
69	d	**DOOMED**	6528	JUNE	113	1140	0.268		14.2	52.3	3290	0.706
70	d	**FINAL**	6509	JUNE	111	1400	0.972		5.5	198	2180	0.055
71	d	**FINAL**	6509	JUNE	117	2210	0.837		5.5	231	2150	0.53
72	d	**FINAL**	6528	JUNE	116	2850	0.494		19.4	173	2760	0.53
73	d	**FINAL**	6528	JUNE	130	2740	0.445		26.2	194	2790	1.09
74	d	**FINAL**	6534	JUNE	115	2670	0.799		19.4	6.07	1640	1.05
75	d	**FINAL**	6534	JUNE	125	2050	0.821		19.4	**6.07**	1570	0.53
76	d	**FINAL**	6535	JUNE	67.1	5200	0.373		96.6	97.4	2780	4.02
77	d	**FINAL**	6535	JUNE	76.9	6000	0.617		110	87	3120	3.61
78	d	**SURVIVED**	6505	JUNE	146	**61.5**	0.815		12.5	28.8	1660	0.44
79	d	**SURVIVED**	6505	JUNE	147	**61.5**	0.931		**1.95**	**6.07**	1700	0.485
80	d	**SURVIVED**	6506	JUNE	191	**61.5**	1.91		1.95	**6.07**	2940	0.349
81	d	**SURVIVED**	6506	JUNE	203	**61.5**	1.82		**1.95**	**6.07**	2790	**0.055**
82	d	**SURVIVED**	6516	JUNE	110	703	0.533		5.5	**6.07**	2850	0.964
83	d	**SURVIVED**	6516	JUNE	120	1190	0.688		5.5	15.8	2760	0.793
84	d	**SURVIVED**	6519	JUNE	115	806	0.353		12.5	39.1	2570	1.13
85	d	**SURVIVED**	6519	JUNE	129	1060	0.493		12.5	43.7	2580	0.706

	A	B	C	D	E	F	G	H	I	J	K	L
86	e	DOOMED	6615	JUNE	185	825	2.17		5.5	22.8	2830	0.879
87	e	DOOMED	6615	JUNE	189	591	2.15		**1.95**	**6.07**	2800	1.22
88	e	DOOMED	6616	JUNE	191	388	1.69		9	28.8	3420	0.44
89	e	DOOMED	6616	JUNE	199	731	1.7		19.4	6.07	3500	1.05
90	e	DOOMED	6622	JUNE	184	572	2.16		9	34.2	2200	0.964
91	e	DOOMED	6622	JUNE	192	684	2.16		**1.95**	28.8	2000	0.706
92	e	DOOMED	6627	JUNE	165	1190	2.49		1.95	15.8	2150	0.158
93	e	DOOMED	6627	JUNE	181	968	2.55		9	6.07	2170	0.255
94	e	SURVIVED	6614	JUNE	187	712	2.13		**1.95**	22.8	2390	0.619
95	e	SURVIVED	6614	JUNE	207	825	2.13		**1.95**	15.8	2340	0.575
96	e	SURVIVED	6618	JUNE	192	977	1.9		9	15.8	2460	0.879
97	e	SURVIVED	6618	JUNE	196	1030	1.94		5.5	39.1	2620	0.53
98	e	SURVIVED	6625	JUNE	193	507	2.28		**1.95**	**6.07**	2250	0.879
99	e	SURVIVED	6625	JUNE	216	121	2.38		19.4	22.8	1990	0.706
100	e	SURVIVED	6633	JUNE	182	164	2.33		1.95	**6.07**	1770	0.349
101	e	SURVIVED	6633	JUNE	181	61.5	2.37		1.95	34.2	1620	0.879
102	e-pool1	FINAL	e-pool1	JUNE	88.8	2770	0.625		33	415	1900	0.879
103	e-pool1	FINAL	e-pool1	JUNE	85.4	2250	0.749		19.4	386	1710	1.05
104	e-pool1	FINAL	e-pool1	JUNE	81.3	2490	0.598		22.8	400	1700	0.964
105	e-pool1	FINAL	e-pool1	JUNE	82.5	2110	0.632		21.1	397	1740	0.879
106	e-pool1	FINAL	e-pool1	JUNE	84.9	3070	0.642		19.4	435	1870	0.879
107	e-pool1	FINAL	e-pool1	JUNE	82.9	2890	0.787		26.2	390	1760	0.793
108	e-pool1	FINAL	e-pool1	JUNE	93.1	2610	0.86		33	404	1730	1.62
109	e-pool1	FINAL	e-pool1	JUNE	93.7	2410	0.833		33	367	1710	1.58
110	e-pool1	FINAL	e-pool1	JUNE	82.4	2610	0.691		43.1	399	2060	1.62
111	e-pool1	FINAL	e-pool1	JUNE	84.2	2670	0.717		43.1	361	1830	1.05
112	e-pool2	FINAL	e-pool2	JUNE	71.9	2110	0.636		26.2	238	954	0.836
113	e-pool2	FINAL	e-pool2	JUNE	78.5	1210	0.635		19.4	257	955	0.793
114	e-pool2	FINAL	e-pool2	JUNE	81.3	2190	**0.221**		22.8	222	991	0.663
115	e-pool2	FINAL	e-pool2	JUNE	86.4	1960	0.37		29.6	231	1000	0.964
116	e-pool2	FINAL	e-pool2	JUNE	81.6	1580	0.601		19.4	235	1020	0.793
117	e-pool2	FINAL	e-pool2	JUNE	83	1810	0.65		15.9	236	920	1.05
118	e-pool2	FINAL	e-pool2	JUNE	83.4	1430	0.47		14.2	244	1050	0.964
119	e-pool2	FINAL	e-pool2	JUNE	85.7	1730	0.672		19.4	235	1010	0.706
120	e-pool2	FINAL	e-pool2	JUNE	84.1	1540	0.452		29.6	246	868	0.663
121	e-pool2	FINAL	e-pool2	JUNE	77.8	1520	0.501		5.5	222	814	0.53
122	f	CONTROL	7354	AUG	170		1.17		26.7	**22.2**	1500	2.94
123	f	CONTROL	7355	AUG	159		1.33		21.7	**22.2**	1980	**0.228**
124	f	CONTROL	7357	AUG	142		1.32		22	**22.2**	1450	**0.228**
125	f	CONTROL	7358	AUG	153		1.24		22	**22.2**	1700	**0.228**
126	f	CONTROL	7359	AUG	166		1.05		3.4	99.8	2080	0.747
127	f	CONTROL	7360	AUG	160		1.23		22.4	67	1790	**0.228**
128	f	CONTROL	7361	AUG	158		1.21		13.7	**22.2**	1920	**0.228**

	A	B	C	D	E	F	G	H	I	J	K	L
129	f	CONTROL	7362	AUG	140		1.05		11	61.7	1930	0.228
130	f	DOOMED	7319	AUG	154		1.38		3.7	22.2	1780	0.228
131	f	DOOMED	7320	AUG	157		1.06		18.5	22.2	2780	0.228
132	f	DOOMED	7322	AUG	135		1.2		9.65	22.2	2700	0.228
133	f	DOOMED	7330	AUG	152		1.18		32.2	22.2	1870	0.228
134	f	DOOMED	7334	AUG	185		1.34		12	22.2	3050	0.584
135	f	DOOMED	7341	AUG	148		1.27		9.33	22.2	2900	0.228
136	f	DOOMED	7345	AUG	155		1.58		18.1	113	1820	0.747
137	f	DOOMED	7350	AUG	153		1.45		32.6	22.2	2520	0.228
138	f	FINAL	7319	AUG	96.2		0.418		9.98	161	4120	1.96
139	f	FINAL	7320	AUG	78.3		0.739		29.3	119	9180	4.39
140	f	FINAL	7322	AUG	75.1		0.465		9.65	232	1900	1.52
141	f	FINAL	7330	AUG	74.8		0.684		20.6	180	4610	3.54
142	f	FINAL	7334	AUG	110		2.01		17.4	143	822	0.684
143	f	FINAL	7341	AUG	98.1		0.465		35.9	140	2170	3.01
144	f	FINAL	7345	AUG	114		0.922		14	140	3390	1.52
145	f	FINAL	7350	AUG	91.3		0.368		40.7	172	1880	3.61
146	f	SURVIVED	7323	AUG	112		1.06		27.4	22.2	2780	0.228
147	f	SURVIVED	7327	AUG	128		0.964		5.83	22.2	2370	0.228
148	f	SURVIVED	7329	AUG	151		1.37		18.5	22.2	2480	0.228
149	f	SURVIVED	7332	AUG	154		1.26		27.8	22.2	2060	0.414
150	f	SURVIVED	7333	AUG	208		1.08		7.08	22.2	2770	0.228
151	f	SURVIVED	7337	AUG	126		1.41		13.7	22.2	1380	0.414
152	f	SURVIVED	7346	AUG	152		1.28		6.14	22.2	1950	0.228
153	f	SURVIVED	7348	AUG	166		1.52		11.6	22.2	1870	0.584
154	e-pool1	FINAL	e-pool1	AUG	75.7		0.191		18.5	203	2230	1.66
155	e-pool1	FINAL	e-pool1	AUG	73.9		0.383		14.3	206	2060	1.22
156	e-pool1	FINAL	e-pool1	AUG	75.9		0.375		22	201	1930	1.81
157	e-pool1	FINAL	e-pool1	AUG	77.8		0.411		13	210	1770	1.37
158	e-pool1	FINAL	e-pool1	AUG	81.5		0.444		18.5	180	1860	1.22
159	e-pool1	FINAL	e-pool1	AUG	80		0.39		19.9	195	1670	1.37
160	pool3	CONTROL	pool3	AUG	159		1.8		22	22.2	506	0.228
161	pool3	CONTROL	pool3	AUG	165		1.6		20.6	56	443	0.228
162	pool3	CONTROL	pool3	AUG	181		1.8		25.6	42.4	526	1.06
163	pool3	CONTROL	pool3	AUG	159		1.74		18.5	22.2	531	0.228
164	pool3	CONTROL	pool3	AUG	154		1.92		31.5	49.7	494	0.906
165	pool3	CONTROL	pool3	AUG	168		1.9		26.4	49.7	493	0.906
166	pool3	CONTROL	pool3	SEP	217		1.07		77.9	15.4	546	0.606
167	pool3	CONTROL	pool3	SEP	205		0.914		77.6	15.4	478	0.783
168	pool3	CONTROL	pool3	SEP	206		0.981		61.7	15.4	521	0.577
169	pool3	CONTROL	pool3	SEP	205		0.917		64.2	25.7	482	0.577
170	e-pool1	FINAL	e-pool1	SEP	94		0.0855		103	314	2510	1.59
171	e-pool1	FINAL	e-pool1	SEP	78.4		0.0855		113	297	2140	1.65

	A	B	C	D	E	F	G	H	I	J	K	L
172	e-pool1	FINAL	e-pool1	SEP	89.8		**0.0855**		87.4	282	2130	1.53
173	d	**S FINAL**	6505	SEP	145		0.225		63.9	**15.4**	718	0.489
174	d	**S FINAL**	6506	SEP	243		1.19		74.1	25.7	358	0.695
175	d	**S FINAL**	6516	SEP	180		0.497		110	15.4	812	0.695
176	d	**S FINAL**	6519	SEP	117		0.0855		173	42.2	1100	0.754
177	d	**S FINAL**	6529	SEP	218		1.17		11.7	38.4	425	0.43
178												
179												
180		**CONTROL**	Animals were non infected. Some animals were irradiated some animals were not.									
181		**INFECTED**	Animals were infected and non-irradiated. Blood samples were taken between 22-24 hours									
182		**SURVIVED**	Animals were infected and irradiated and were healthy up to 14d. Blood samples were taken at 22-24 hours									
183		**DOOMED**	Animals were infected and irradiated and became moribund and were euthanized or died.Blood samples were taken at 22-24 hou									
184		**S FINAL**	Animals were infected and irradiated and were healthy at 144 hours when blood samples were taken.									
185		**FINAL**	Animals were infected and irradiated became moribund and were euthanized.Blood samples were taken before euthanasia.									
186		**BLUE NUMBER**	RBM gave the value as HIGH. We sobstituted the value with the highest value for the day for the specific analyte.									
187		**RED NUMBER**	RBM gave the value as LOW. We sobstituted the value with the lowest value for the day for the specific analyte.									
188												

	M	N	O	P	Q	R	S	T	U	V	W
1											
2											
3											
4	FGF-9	FGFb	Fibrinogen	GCP-2	GM-CSF	Growth Horm	GST	Haptoglobin	IFNg	IgA	IL-10
5	ng/ml	ng/ml	ug/ml	ng/ml	pg/ml	ng/ml	ng/ml	ug/ml	pg/ml	ug/ml	pg/ml
6	0.502	0.552		0.279	0.565	0.11	4.39		54.1		139
7	1	1.93		0.506	2.32	0.0845	4.02		77		170
8	0.211	1.93		0.691	1.12	0.0931	8.76		65.4		79.5
9	0.917	2.88		0.315	0.565	0.163	10.9		272		139
10	1.13	0.552		0.374	0.565	0.137	2.03		77		170
11	0.693	1.47		0.829	1.12	0.145	7.52		145		221
12	0.784	0.552		0.266	1.7	0.0931	4.39		77		159
13	0.211	0.552		0.194	1.7	0.0342	1.14		54.1		159
14	5.09	1.93		2.26	12.1	0.0674	7.11		466		2790
15	8.53	5.85		3.49	40.2	0.0931	11.7		687		4340
16	3.97	3.85		0.864	8.46	0.106	6.91		396		2780
17	10.8	37.7		3.68	93.1	0.248	15		1160		7310
18	10.2	21.7		3.38	61	0.106	13		1050		7830
19	2.42	3.85		1.26	5.79	0.128	8.13		300		1650
20	1.39	3.36		1.32	4.35	0.171	6.31		258		596
21	1.3	1.01		1.69	1.7	0.0845	6.71		132		569
22	1.13	0.552		0.308	6.54	0.0589	11.7		258		1610
23	1.35	3.25		1.56	6.42	0.0754	5.2	3.28	167	725	1130
24	0.999	1.13		0.789	5.86	0.0573	7.13	3.74	129	551	549
25	1.06	1.13		0.517	6.14	0.0521	5.94	4.1	107	627	421
26	0.843	1.13		0.917	3	0.078	4.15	2.68	77.9	669	241
27	2.18	2.59		0.715	7.57	0.078	6.24	1.33	160	855	1570
28	1.6	3.89		0.341	5.31	0.106	6.53	3.18	205	653	1190
29	2.05	2.24		0.508	7.57	0.119	7.72	2.53	205	704	1570
30	1.59	5.02		2.86	17.7	0.108	3.49		131		1510
31	1.45	12.8		2.78	12.8	0.205	5.99		56.4		1620
32	1.14	0.682		1.53	9.83	0.187	6.67		22.8		237
33	1.14	10		2.94	21.7	0.196	3.65		88.1		1490
34	1.52	5.02		0.314	2.75	0.168	4.98		64.6		169
35	0.815	**0.682**		0.66	0.991	0.148	3		39.5		102
36	0.815	1.79		1.12	0.53	0.241	8.05		**14.1**		120
37	0.815	2.85		0.452	**0.53**	0.338	7.36		48		132
38	0.467	3.39		0.387	**0.53**	0.128	1.75		14.1		71.7
39	0.815				**0.53**				39.5		156
40	1.45	3.93		0.401	3.2	0.187	4.64		95.6		243
41	**0.268**	0.682		0.318	**0.53**	0.187	2.37		27.1		59.7
42	0.467	1.79		1.12	1.43	0.187	3.65		22.8		193

	M	N	O	P	Q	R	S	T	U	V	W
43	2.97				67.2				131		1420
44	3.67	46.8		3.17	43.2	0.688	12.2		187		2560
45	**0.268**	10		1.88	3.65	0.386	8.39		88.1		144
46	0.815	5.02		1.57	0.53	0.314	4.98		72.6		162
47	**0.268**	3.93		2.3	**0.53**	0.25	3.98		39.5		83.6
48	**0.268**	7.23		0.329	2.3	0.275	9.43		14.1		96.6
49	**0.268**	2.32		1.46	**0.53**	0.241	3		14.1		114
50	**0.268**	0.682		2.67	**0.53**	0.168	4.98		**14.1**		**47.7**
51	0.646	2.85		1.86	0.991	0.214	8.22		22.8		59.7
52	2.31	7.23		2.34	4.11	0.187	3.98		76.5		575
53	0.467	10.6		3.23	0.53	0.168	5.15		14.1		89.6
54	0.467	4.47		1.91	3.2	0.168	4.64		39.5		193
55	0.467	2.85		3.14	8.86	0.205	4.64		48		250
56	0.268	9.45		3.7	4.57	0.205	3.65		18.5		193
57	0.467	5.02		1.27	**0.53**	0.148	6.33		**14.1**		47.7
58	**0.268**	6.67		1.53	1.43	0.275	5.99		22.8		132
59	0.646	8.34		1.55	2.3	0.241	5.32		64.6		181
60	0.732	2.85		2.71	1.43	0.168	7.36		60.5		71.7
61	**0.268**	5.02		1.76	2.3	0.378	3.65		127		132
62	**0.0695**	2.97	4290	4.25	6.06	0.0996	1.92	38.4	28.1	99.1	115
63	0.0695	8.38	5540	5.93	5.51	0.174	4.8	38	31.3	109	115
64	0.246	1.3	5690	1.61	3.12	0.208	3.02	36.4	68.4	126	75.7
65	**0.0695**	5.81	6810	1.64	**1.59**	0.252	3.02	39.3	24.3	138	60.5
66	0.246	3.72	2650	2.47	13.1	0.294	4.27	34.2	76.2	107	245
67	0.495	0.151	3090	2.53	10.6	0.151	3.38	35.2	130	128	256
68	0.666	2.97	3660	1.92	6.6	0.284	5.16	35.3	168	81.5	195
69	0.722	6.14	5200	1.93	7.12	0.219	2.66	36.5	76.2	82.7	215
70	0.61	13.2	**137**	17.4	36.8	0.284	4.45	44.9	213	105	2750
71	0.375	14	**137**	22.5	41.4	0.315	4.27	47.1	107	110	2650
72	0.939	23.4	**137**	37.9	74.9	0.483	6.9	32.8	243	107	4390
73	1.75	28	**137**	41.7	70	0.558	9.49	34.4	243	110	4170
74	0.831	16.6	137	19.7	83.3	0.405	7.25	35.8	122	186	1380
75	1.25	12.6	**137**	20.7	101	0.366	6.21	39.3	122	203	1370
76	2.08	104	6370	27	48.9	0.668	15.3	26.9	156	251	1390
77	1.99	102	9470	30.5	51.8	0.65	10.3	28.2	328	276	1390
78	**0.0695**	2.18	4440	0.562	**1.59**	0.052	1.73	36.6	24.3	92.1	**18.9**
79	**0.0695**	1.3	4580	0.546	1.59	0.126	2.29	33	31.3	95.5	33.3
80	**0.0695**	1.3	6790	0.757	1.59	0.0251	0.703	44	**3.44**	147	**18.9**
81	**0.0695**	**0.151**	5670	0.729	1.59	**0.0251**	**0.703**	47.1	**3.44**	156	44.8
82	0.553	**0.151**	4960	2.28	7.12	0.151	1.14	35.4	36.5	71.6	115
83	0.246	0.151	5370	2.28	8.66	**0.0251**	3.02	39	31.3	80.3	95.6
84	**0.0695**	5.14	2900	1.57	6.6	0.0996	2.29	25	107	117	135
85	0.495	1.3	4020	1.54	7.64	0.197	4.8	26.1	76.2	132	95.6

	M	N	O	P	Q	R	S	T	U	V	W
86	**0.0695**	**0.151**	8170	1.17	4.36	0.138	3.02	54.7	17.4	174	105
87	0.246	1.3	7650	1.12	4.36	0.126	2.29	53.4	20.8	192	105
88	**0.0695**	2.97	5370	0.777	1.59	0.174	5.16	43.8	**3.44**	153	55.4
89	0.312	3.72	5710	0.775	4.94	0.23	2.66	44.3	31.3	168	105
90	**0.0695**	2.18	7070	1.67	1.59	0.126	4.45	54.1	**3.44**	164	75.7
91	**0.0695**	1.3	7510	1.61	5.51	0.0699	1.53	54.9	**3.44**	169	65.6
92	0.0695	0.151	7160	1.76	4.36	0.052	3.38	50.8	28.1	185	125
93	**0.0695**	1.3	12200	1.72	1.59	0.151	1.92	55.6	17.4	177	75.7
94	0.495	1.3	9850	1.28	7.64	0.126	2.66	55.2	31.3	182	39.2
95	**0.0695**	2.97	8240	1.28	**1.59**	0.0996	1.14	55.9	10.4	202	**18.9**
96	0.666	**0.151**	7580	1.25	9.66	0.174	4.27	50.3	68.4	184	105
97	0.246	7.12	8890	1.24	8.66	0.197	7.25	52.2	27.8	205	65.6
98	**0.0695**	**0.151**	5770	0.728	3.12	0.0251	1.92	55.4	3.44	186	105
99	0.375	0.151	6450	0.698	8.66	0.219	2.29	52.8	36.5	180	85.7
100	**0.0695**	0.151	8930	1.38	**1.59**	0.113	3.38	54.6	**3.44**	184	18.9
101	**0.0695**	2.18	7480	1.29	1.59	0.0251	3.2	52.6	**3.44**	176	**18.9**
102	1.45	27.1	5360	13.5	32.2	0.425	17.5	38.1	317	110	4650
103	1.35	23.4	5830	17.5	34	0.366	9.32	37.2	246	98.8	4130
104	1.35	28.3	5790	13.8	31.2	0.325	18.8	36.1	269	98.8	4510
105	1.45	21.7	8280	17.2	28	0.415	12.2	39.1	272	103	4410
106	1.45	25.7	4280	14	40.5	0.445	16.4	37.5	317	99.3	4830
107	1.25	21.1	4010	13.4	34	0.366	9.66	39.2	298	107	4800
108	1.75	22.3	6250	15.3	42.4	0.325	26.8	40.2	328	106	4430
109	1.85	22.8	5980	15.9	35.9	0.445	14.4	38.7	302	106	4580
110	1.55	26.2	5440	14.2	32.2	0.425	24.5	36.6	328	105	5750
111	1.45	26.8	6140		41.4	0.549	13.7	39.7	377	107	4780
112	1.65	22.3	6730	15.2	34.9	0.405	14.4	37.2	332	98.4	2390
113	1.55	24	8010	19.2	25.7	0.386	11	35	250	96.7	2160
114	1.35	29.7	4550	16.8	34	0.425	14.4	33.5	228	101	2420
115	1.25	24.5	5540	16.5	29.9	0.425	8.28	35.9	257	100	2320
116	1.35	26.8	6730	15.8	31.2	0.445	9.32	35	243	97.1	2330
117	0.939	21.1	4930	19.8	28.5	0.366	8.46	38.6	175	92.8	2250
118	1.04	26	5710	17.1	29.4	0.356	7.25	36.8	175	96.6	2350
119	1.25	24	6500	19.1	28.5	0.445	5.16	36	175	92.7	2120
120	0.831	20.5	6760	26.5	24.3	0.335	12.4	37	265	104	2050
121	1.15	21.4	5940	20.1	28.5	0.284	6.21	35.4	145	94	2330
122	**0.281**	2.89	2390	0.432	**4.12**	0.435	1.81	53	**18.6**	209	**143**
123	**0.281**	**0.377**	2910	0.718	**4.12**	**0.0261**	0.449	45.2	**18.6**	89.5	**143**
124	0.457	**0.377**	3030	0.424	17.1	**0.0261**	**0.0798**	53	18.6	94.6	**143**
125	0.876	**0.377**	2620	0.615	14.4	**0.0261**	0.349	14.3	**18.6**	95.4	**143**
126	0.457	**0.377**	2710	0.353	**4.12**	**0.0261**	**0.0798**	45.1	**18.6**	117	**143**
127	**0.281**	**0.377**	2580	0.173	**4.12**	**0.0261**	2.87	28.3	**18.6**	88.8	**143**
128	0.876	**0.377**	2580	0.31	13.5	**0.0261**	0.554	52	34.1	101	**143**

	M	N	O	P	Q	R	S	T	U	V	W
129	0.457	0.377	3680	1.01	6.51	0.0261	0.554	58.9	18.6	109	143
130	0.281	0.377	14000	1.13	4.12	0.0261	0.0798	71.3	18.6	110	143
131	0.281	0.377	5070	1.5	18	0.0261	0.0798	60.2	18.6	88.8	143
132	0.281	0.377	9020	1.38	4.12	0.0261	0.349	67.7	18.6	101	143
133	0.457	0.377	5250	1.82	12.6	0.0261	0.253	76.6	58	184	143
134	0.69	0.377	9690	1.02	4.12	0.0579	0.554	84	18.6	170	143
135	0.281	0.377	5910	1.22	6.51	0.0261	0.0798	80	46.5	92.2	143
136	0.281	0.377	11400	1.55	5.36	0.0261	1.42	82.3	18.6	122	143
137	0.457	0.691	5910	1.43	4.12	0.105	0.449	67.7	18.6	93.1	143
138	1.78	0.377	3430	15.1	30.3	0.0261	3.25	57.7	46.5	70	2410
139	1.59	0.377	4900	26.3	38.6	0.0579	1.55	60.4	145	143	4740
140	1.83	0.691	2580	9.65	21.4	0.0261	2.74	51.5	175	87.7	8120
141	1.47	1.03	2970	29	33.4	0.15	0.0798	49.5	89.4	324	5490
142	0.583	0.377	12500	1.34	13.5	0.0261	0.904	70.8	18.6	189	738
143	1.19	0.691	2910	6.8	24.7	0.0676	3.13	61.9	46.5	179	1810
144	2.58	0.377	8450	5.22	34.1	0.0261	1.29	71.7	74.1	369	1620
145	1.83	1.19	3290	12.1	34.1	0.305	2.61	56.2	162	128	4300
146	1.19	0.377	5910	0.981	14.4	0.0261	1.03	79	52.3	92.1	143
147	0.876	0.377	6170	0.737	16.2	0.0261	0.0798	64.6	18.6	142	143
148	0.281	0.377	6770	0.199	6.51	0.0261	0.554	66.1	18.6	106	143
149	1.19	0.377	5450	0.31	4.12	0.0261	0.554	82.7	18.6	171	143
150	0.281	0.377	9020	0.769	4.12	0.0261	0.0798	65	18.6	207	143
151	0.876	0.377	5450	1.23	6.51	0.0261	0.0798	75.1	18.6	177	143
152	0.69	0.377	9020	1.4	4.12	0.0261	0.0798	77.2	18.6	114	143
153	1.19	0.377	5910	0.379	6.51	0.0261	1.42	78.4	18.6	106	143
154	2	0.377	2860	15.2	43	0.0261	11.3	53.2	118	86.3	5650
155	1.47	0.377	3030	15.8	40.1	0.0376	13.6	63.2	123	87.6	5630
156	2.95	0.691	4450	13.6	49.9	0.0376	15.2	63.7	171	88.7	5810
157	2.48	0.377	2670	12.9	56.7	0.0261	12.1	60	175	85.6	5300
158	1.33	0.377	3290	13	44.4	0.0771	17.1	63.2	210	97.8	5250
159	1.47	0.377	4320	13.8	37.1	0.0579	16.6	60.5	150	95.2	4920
160	0.281	0.377	1150	1.05	4.12	0.0261	0.0798	16.7	18.6	193	143
161	0.457	0.377	1050	0.945	8.63	0.0261	0.449	14.6	18.6	177	143
162	0.281	0.377	1210	1	4.12	0.0261	1.29	17.2	18.6	209	143
163	0.281	0.377	1060	1.08	4.12	0.0261	0.664	17.7	18.6	193	143
164	0.281	0.377	996	0.975	4.12	0.0261	4.12	15.2	18.6	184	143
165	1.33	0.377	1140	0.963	10.6	0.0261	0.449	16.3	52.3	185	143
166	0.161	0.455	1810	0.969	7.22	0.0496	0.954	12.4	16.8	160	49.1
167	0.417	0.412	2060	0.934	4.7	0.0645	2.33	13.9	28.6	158	49.1
168	0.974	0.19	1560	0.905	4.7	0.11	2.88	14.6	34.6	156	74.9
169	0.417	0.19	1770	0.893	12.3	0.00964	2.47	16.4	1.83	158	49.1
170	2.2	0.873	4570	18.4	44.7	0.125	6.79	52.6	138	74.6	6640
171	2.27	1.05	5070	16.1	46.1	0.14	4.67	45.6	138	68.9	6260

	M	N	O	P	Q	R	S	T	U	V	W
172	2.97	0.838	4930	15.6	48.8	0.11	3.85	50.6	191	71.3	6150
173	0.761	**0.19**	643	0.472	5.96	0.0194	1.22	12.7	**1.83**	89.4	**49.1**
174	0.761	0.365	2340	0.0471	**4.7**	0.0348	2.05	29.7	11.1	116	**49.1**
175	0.417	0.19	1120	1.19	4.7	0.057	3.16	58.9	**1.83**	55.3	49.1
176	0.832	0.365	122	1.66	7.22	0.0794	3.85	62.2	28.6	101	74.9
177	0.832	**0.19**	3550	0.453	6.59	0.0645	0.561	74	53.4	122	**49.1**
178											
179											
180											
181											
182											
183	s										
184											
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188											

	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ
1													
2													
3													
4	IL-11	IL-12p70	IL-17	IL-18	IL-1a	IL-1b	IL-2	IL-3	IL-4	IL-5	IL-6	IL-7	Insulin
5	pg/ml	ng/ml	ng/ml	ng/ml	pg/ml	pg/ml	pg/ml	pg/ml	pg/ml	ng/ml	pg/ml	ng/ml	uIU/ml
6	91.5	0.139	0.0129	1.18	223	0.208	7.54	16.5	26.9	0.0891	15	0.198	
7	82.2	0.243	0.0344	0.98	302	0.172	15.9	26.4	20.1	0.112	22.2	0.198	
8	91.5	0.166	0.0129	1.22	252	0.208	9.52	19.5	18.4	0.0891	16	0.198	
9	96.3	0.447	0.0684	1.1	207	0.276	11.6	33.1	39.8	0.112	33.5	0.198	
10	82.2	0.0545	0.0235	1.24	199	0.276	7.54	19.8	23.6	0.156	14	0.198	
11	111	0.243	0.0569	1.26	367	0.225	12.6	34.3	20.1	0.134	18	0.198	
12	140	0.0848	0.0235	1.1	210	0.243	13.7	17.6	69.5	0.0891	17	0.198	
13	63.7	0.0848	0.0569	0.856	103	0.243	13.7	12.2	20.1	0.0433	18	0.198	
14	487	1.24	0.152	2.24	1130	0.341	63.9	299	115	0.222	1900	0.198	
15	690	1.78	0.272	2.55	1710	0.446	116	500	158	0.244	7100	0.351	
16	318	1.02	0.134	1.78	1060	0.341	59.9	273	133	0.2	731	0.198	
17	917	2.67	0.509	1.84	3040	0.77	143	792	251	0.411	**78800**	0.487	
18	852	2.32	0.52	1.93	2880	0.309	199	876	243	0.244	78800	0.324	
19	278	0.849	0.0684	1.75	902	0.372	30.1	172	103	0.2	527	0.198	
20	228	0.574	0.116	1.58	518	0.372	22.8	91.3	83.4	0.233	269	0.198	
21	238	0.294	0.0344	1.56	445	0.341	25.2	71.8	42.9	0.178	241	0.198	
22	263	0.625	0.0978	1.26	855	0.172	45.4	176	77.9	0.134	365	0.198	
23	221	0.578	0.0746	1.57	535	0.371	27.4	112	47.3	0.152	209	0.0946	
24	123	0.39	0.0896	1.11	313	0.404	19.5	52.3	46.3	0.0762	230	0.0341	
25	150	0.321	0.0821	1.14	229	0.139	23	51.7	36.3	0.0614	93.7	0.0225	
26	105	0.338	0.0265	1.37	219	0.292	16.2	40.5	40.3	0.106	110	0.0225	
27	224	0.941	0.0821	2.09	635	0.292	39.5	164	70.1	0.159	330	0.118	
28	244	0.72	0.0746	1.66	498	0.338	24.7	129	48.3	0.121	209	0.0655	
29	191	0.803	0.136	1.66	679	0.268	66.7	172	101	0.121	532	0.0618	
30	85.5	0.494	1.24	1.15	236	0.218	48.3	160	99.5	0.0649	11900	0.87	5.26
31	13.1	0.402	0.719	1.99	190	0.57	39.6	136	70.2	0.116	6540	0.252	10.8
32	195	0.283	0.121	2.19	94	0.325	52.6	82.4	64.8	0.0566	1360	0.618	3.15
33	55.1	0.371	0.817	1.84	202	0.542	39.6	137	64.8	0.133	6600	0.618	4.33
34	47.3	0.283	0.121	1.13	164	0.626	39.6	50.3	75.4	0.032	8.07	0.89	1.77
35	33.3	0.184	0.061	0.974	153	0.179	30	35.1	44.1	0.0817	14.1	0.87	0.766
36	47.3	0.12	0.0435	1.1	169	0.325	**6.19**	25.4	34.1	0.0649	4.79	0.48	2.06
37	18.2	0.133	**0.0168**	0.889	87.7	0.57	**6.19**	29.5	37.5	0.0159	6.48	0.362	2.85
38	13.1	0.108	**0.0168**	0.705	115	0.883	10.2	28.5	27.1	0.0484	**4.79**	0.469	1.62
39	38.4	0.184	0.0697		258		**6.19**	25.4	53.3		9.61	0.618	
40	55.1	0.133	**0.0168**	1.02	115	0.39	74.2	45.2	108	0.032	11.1	0.533	2.45
41	5.39	0.0276	**0.0168**	0.932	71.6	0.255	39.6	23.3	40.8	0.0817	6.48	0.185	0.882
42	23.2	0.133	**0.0168**	1.02	158	0.57	10.2	45.2	40.8	0.0484	140	0.252	2.27

	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ
43	118	0.587	0.865		750		39.6	162	94.9		**11900**	0.576	
44	123	1.01	1.15	2.11	363	1.4	180	181	133	0.379	11500	1.03	6.75
45	102	0.297	0.0347	1.66	195	0.57	18.2	64.3	56.3	0.2	102	0.555	2.88
46	55.1	0.432	0.0871	1.28	118	0.513	18.2	48	80.4	0.133	46.7	0.983	2.41
47	47.3	0.283	**0.0168**	1.37	195	0.39	**6.19**	48.4	59.2	0.0986	67.2	1.03	2.62
48	47.3	0.158	0.0168	1.42	118	0.57	**6.19**	38.5	27.1	0.166	60.1	0.469	3.15
49	2.77	0.184	**0.0168**	0.974	74.9	0.179	**6.19**	23.3	40.8	0.032	**4.79**	0.138	1.43
50	**2.77**	**0.0276**	**0.0168**	1.32	136	0.325	**6.19**	6.15	15	0.116	**4.79**	0.459	1.06
51	2.77	0.043	0.0168	1.32	164	0.39	10.2	10.9	47.2	0.0484	6.48	0.448	2.82
52	82.8	0.525	0.156	1.46	210	0.733	52.6	93.6	59.2	0.258	291	1.48	3.01
53	18.2	0.204	**0.0168**	1.42	106	0.68	18.2	64.7	27.1	0.133	220	0.448	2.95
54	96.2	0.108	0.0871	2.26	166	0.39	39.6	55.3	34.1	0.0986	1540	0.241	1.62
55	35.8	0.402	0.121	1.39	236	0.325	82.6	77.3	34.1	0.107	547	0.618	1.69
56	23.2	0.204	0.104	1.84	112	0.883	**6.19**	62.1	30.6	0.149	486	0.426	3.21
57	**2.77**	0.0276	0.0347	1.32	147	0.179	18.2	45.2	53.3	0.0817	137	0.34	0.92
58	50.9	0.108	0.0258	1.21	106	0.453	**6.19**	33.6	53.3	0.116	90.9	0.0845	2.55
59	49	0.228	0.0697	1.13	118	0.325	65.6	54.4	47.2	0.166	60.1	0.597	2.13
60	13.1	0.0824	0.0258	1.62	136	0.707	**6.19**	37.5	40.8	0.116	155	0.565	3.54
61	33.3	0.255	0.0523	1.46	112	0.453	31.3	41.4	90.1	0.183	77	0.533	2.41
62	30.1	**0.337**	0.0718	1.71	72.4	0.353	**11.6**	34.1	**17**	0.181	223	**0.0709**	**0.558**
63	17.2	**0.337**	0.0274	1.5	58.3	0.437	**11.6**	34.1	**17**	0.291	239	**0.0709**	**0.558**
64	**17.2**	**0.337**	0.0493	1.5	48.5	0.375	19.6	28.7	**17**	0.125	127	**0.0709**	**0.558**
65	**17.2**	**0.337**	**0.00486**	1.69	53.5	0.264	**11.6**	26	**17**	0.232	132	**0.0709**	**0.558**
66	139	**0.337**	0.0346	1.69	81.4	0.556	26.4	37.6	56.5	0.28	183	0.0912	3.62
67	124	**0.337**	0.0493	1.57	85.8	0.309	26.4	37.6	**17**	0.367	204	0.118	1.7
68	180	**0.337**	0.0949	1.64	103	0.353	50.3	57.8	78.1	0.291	157	0.0709	**0.558**
69	154	**0.337**	0.126	1.78	94.5	0.556	26.4	54.6	**17**	0.168	141	0.144	0.558
70	180	0.628	1.56	3.21	332	0.517	157	169	118	0.154	42000	0.131	1.7
71	226	0.729	1.66	3.01	362	0.437	157	164	148	0.232		0.158	2.21
72	339	0.956	1.81	4.28	2180	1.4	218	192	137	0.207	139000	0.144	0.558
73	329	0.919	1.73	4.72	2160	1.5	238	212	162	0.181	161000	0.292	1.61
74	247	0.521	1.12	1.4	590	0.875	168	151	118	0.207	31000	0.184	**0.558**
75	293	0.521	1.24	1.24	645	0.613	137	161	83	0.207	32900	0.211	**0.558**
76	483	0.455	1.37	2.03	1390	2.81	147	156	110	1.36	16000	0.415	3.5
77	503	0.385	1.61	1.95	1400	2.8	147	151	126	1.3	18000	0.312	3.23
78	**17.2**	**0.337**	**0.00486**	1.18	155	**0.0497**	**11.6**	1.71	**17**	0.125	9.09	**0.0709**	**0.558**
79	**17.2**	**0.337**	**0.00486**	1.04	171	**0.0497**	**11.6**	**1.71**	**17**	0.0773	14.4	**0.0709**	**0.558**
80	**17.2**	**0.337**	0.00486	1.18	63.1	0.113	**11.6**	15.1	**17**	0.125	25.7	**0.0709**	**0.558**
81	**17.2**	**0.337**	**0.00486**	0.798	63.1	0.0497	**11.6**	10.8	**17**	**0.0591**	24.9	**0.0709**	**0.558**
82	62.6	**0.337**	0.0642	1.69	122	0.264	19.6	34.1	**17**	0.257	244	**0.0709**	**0.558**
83	109	**0.337**	0.119	1.53	107	0.517	61.6	36.5	**17**	0.0941	221	**0.0709**	**0.558**
84	154	**0.337**	0.142	1.3	72.4	0.375	26.4	24.9	36.6	0.28	74	**0.0709**	**0.558**
85	124	**0.337**	0.0642	1.32	48.5	0.458	38.7	23.4	50.4	0.207	68.6	**0.0709**	**0.558**

	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ
86	17.2	0.337	0.00486	1.48	109	0.192	38.7	27.2	17	0.195	105	0.0709	0.558
87	17.2	0.337	0.0949	0.939	115	0.167	61.6	27.2	17	0.154	89.3	0.0709	0.558
88	17.2	0.337	0.00486	1.45	143	0.309	11.6	19.6	17	0.168	66.8	0.0709	0.558
89	52.1	0.337	0.0642	1.6	151	0.396	72.6	24.9	62.3	0.0591	81.2	0.0709	0.558
90	17.2	0.337	0.00486	1.13	103	0.309	11.6	18.1	17	0.168	172	0.0709	0.558
91	17.2	0.337	0.00486	0.834	81.4	0.141	11.6	18.9	17	0.0591	155	0.0709	0.558
92	17.2	0.337	0.0567	1.18	101	0.0497	50.3	36.5	17	0.0941	212	0.0709	0.558
93	17.2	0.337	0.0203	1.21	88	0.0497	11.6	32.2	17	0.125	185	0.0709	0.558
94	17.2	0.337	0.0493	1.07	63.1	0.0497	11.6	14	50.4	0.14	65	0.0709	0.558
95	17.2	0.337	0.00486	1.07	38.1	0.113	11.6	10.1	17	0.0941	67.7	0.0709	0.558
96	52.1	0.337	0.0795	1.45	139	0.217	11.6	21.9	17	0.0591	66.8	0.0709	0.558
97	24	0.337	0.00486	1.45	98.7	0.353	11.6	12.2	17	0.28	52.5	0.0709	0.558
98	17.2	0.337	0.00486	1.5	92.3	0.113	26.4	18.9	17	0.181	43.7	0.0709	0.558
99	17.2	0.337	0.0795	1.24	107	0.309	105	16.6	50.4	0.154	52.5	0.0709	0.558
100	17.2	0.337	0.00486	1.13	60.7	0.0497	11.6	14.4	17	0.0591	112	0.0709	0.558
101	24	0.337	0.00486	1.3	76.9	0.167	11.6	7.89	17	0.125	98.4	0.0709	0.558
102	380	0.768	1.92	2.83	411	1.44	198	184	141	0.456	38500	0.171	4
103	257	0.607	1.85	2.58	388	1.2	208	174	118	0.447	50800	0.211	4
104	360	0.807	1.99	2.63	377	1.23	213	174	148	0.466	40200	0.292	3.81
105	303	0.648	1.77	2.73	356	1.16	188	175	175	0.408	53100	0.211	3.87
106	350	1.06	2.03	2.9	415	1.21	223	193	162	0.503	40500	0.333	3.37
107	411	0.768	1.76	2.9	411	1.31	267	201	134	0.456	45300	0.299	3.1
108	324	0.882	2.06	2.97	464	1.44	208	185	200	0.572	39900	0.265	4
109	339	0.919	1.96	3.13	407	1.19	296	181	162	0.547		0.346	3.1
110	401	1.03	2.1	3	468	1.41	253	212	188	0.538	43100	0.387	4.58
111	380	1.2	1.85	2.93	415	1.27	277	208	197	0.484		0.251	4.23
112	319	0.729	2.27	1.95	366	1.16	188	173	134	0.456	37600	0.278	5.45
113	288	0.607	2.14	1.74	339	1.04	188	149	148	0.408		0.224	4.91
114	314	0.689	2.14	1.78	313	1.16	168	152	126	0.447	38800	0.251	5.24
115	278	0.565	2.17	1.74	369	1.16	208	169	162	0.447	49400	0.184	5.13
116	175	0.648	2.07	1.87	347	1	162	161	110	0.367	35900	0.158	4.91
117	226	0.337	2.14	1.62	324	0.941	126	147	134	0.493		0.144	4.41
118	257	0.385	2.01	1.74	337	1.04	147	137	130	0.484	37900	0.191	4
119	206	0.521	1.72	1.74	293	0.973	116	134	92.4	0.408		0.105	3.93
120	185	0.521	1.87	1.82	328	1.02	88.9	142	118	0.346	54900	0.144	3.62
121	206	0.455	1.85	1.55	313	0.973	126	146	110	0.428	52200	0.0912	2.96
122	3.92	0.0682	0.0561	0.00777	40.6	0.0689	12.5	5.32	71.1	0.0295	8.46	0.0322	<LOW>
123	3.92	0.0682	0.0561	0.00777	93.7	0.0266	12.5	5.32	71.1	0.0295	8.46	0.0508	<LOW>
124	3.92	0.0682	0.0561	0.723	87.7	0.0266	12.5	5.32	71.1	0.0295	8.46	0.0687	<LOW>
125	12.7	0.0682	0.0561	0.00777	118	0.0689	12.5	5.32	71.1	0.0295	16.9	0.0598	<LOW>
126	3.92	0.198	0.107	0.00777	44.4	0.135	12.5	5.32	71.1	0.0295	8.46	0.0322	<LOW>
127	3.92	0.0682	0.0561	0.64	5.97	0.119	12.5	5.32	71.1	0.105	8.46	0.0322	<LOW>
128	50.1	0.299	0.0561	0.00777	12	0.0266	30.4	5.32	108	0.0295	10	0.0687	<LOW>

	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ
129	3.92	0.0682	0.0561	0.00777	261	0.0266	12.5	5.32	71.1	0.0295	14.3	0.0508	<LOW>
130	12.7	0.0682	0.0561	0.00777	32.5	0.0266	12.5	5.32	71.1	0.0295	166	0.143	<LOW>
131	35.5	0.516	0.0771	0.00777	158	0.0689	12.5	8.5	71.1	0.0705	98.2	0.134	<LOW>
132	19.6	0.0682	0.155	0.373	46.3	0.0689	21.7	14.4	71.1	0.0295	171	0.124	<LOW>
133	35.5	0.39	0.197	0.168	80.1	0.135	81.5	22	71.1	0.0705	221	0.143	<LOW>
134	26.2	0.0682	0.0561	0.882	109	0.0266	63.8	10.3	71.1	0.23	99.3	0.162	<LOW>
135	26.2	0.0682	0.0561	0.00777	14.4	0.0266	12.5	9.71	71.1	0.0295	106	0.0322	<LOW>
136	3.92	0.0682	0.0561	1.18	53.6	0.31	12.5	10.9	71.1	0.0295	234	0.0322	<LOW>
137	63.7	0.0682	0.107	0.723	75.4	0.135	12.5	16.2	71.1	0.0295	193	0.0508	<LOW>
138	316	2.73	1.39	1.83	211	0.268	195	139	193	0.471	25000	0.572	<LOW>
139	376	2.81	1.22	3.63	298	0.135	195	152	210	0.802	74400	0.433	<LOW>
140	428	2.81	1.25	1.32	231	0.826	132	128	202	0.342	35300	0.376	<LOW>
141	376	2.52	1.24	5.27	238	0.391	195	135	175	0.72	55900	0.395	<LOW>
142	103	1.37	0.896	0.882	115	0.166	30.4	41.3	71.1	0.23	3120	0.0831	<LOW>
143	218	1.7	0.939	4.95	209	0.103	90.2	72.3	71.1	0.656	3820	0.221	<LOW>
144	206	1.86	0.794	2.06	188	0.119	90.2	73.9	161	0.446	17000	0.337	<LOW>
145	491	2.56	1.38	1.58	238	0.43	225	105	145	0.519	21000	0.405	<LOW>
146	77	0.299	0.236	0.168	166	0.0266	63.8	12.7	145	0.0295	78.9	0.0322	<LOW>
147	206	0.39	0.133	2.79	48.2	0.0266	30.4	22	92	0.0295	82.3	0.153	<LOW>
148	3.92	0.0682	0.0771	0.723	44.4	0.0266	12.5	5.32	71.1	0.0295	34.4	0.0831	<LOW>
149	50.1	0.299	0.0771	0.373	38.6	0.0266	12.5	12.7	128	0.0295	67.4	0.0508	<LOW>
150	12.7	0.0682	0.0561	0.168	30.4	0.0689	12.5	5.32	71.1	0.0295	58.2	0.0687	<LOW>
151	35.5	0.0682	0.0771	0.723	53.6	0.103	12.5	5.32	71.1	0.105	117	0.143	<LOW>
152	3.92	0.0682	0.0561	0.168	14.4	0.166	12.5	5.32	108	0.0295	107	0.0322	<LOW>
153	19.6	0.0682	0.0561	0.168	5.97	0.135	12.5	5.32	71.1	0.138	58.2	0.0508	<LOW>
154	507	3.05	1.45	2.49	368	0.693	240	148	193	0.471	45600	0.49	<LOW>
155	434	2.6	1.44	2.69	360	0.637	275	154	225	0.471	46600	0.433	<LOW>
156	491	3.05	1.56	2.69	372	0.704	254	160	206	0.421	45900	0.545	<LOW>
157	411	3.01	1.42	2.28	347	0.637	140	152	236	0.421	42400	0.508	<LOW>
158	411	2.77	1.38	2.39	333	0.615	268	144	218	0.421	45500	0.452	<LOW>
159	328	2.56	1.29	2.59	297	0.591	164	126	156	0.434	36100	0.357	<LOW>
160	3.92	0.0682	0.0561	0.168	108	0.0266	12.5	5.32	71.1	0.0295	8.46	0.0322	<LOW>
161	3.92	0.198	0.107	0.723	129	0.0266	44.9	5.32	71.1	0.105	8.46	0.0322	<LOW>
162	3.92	0.0682	0.0561	0.723	81.6	0.135	12.5	5.32	71.1	0.105	8.46	0.0322	<LOW>
163	3.92	0.25	0.0933	0.554	126	0.0266	12.5	5.32	71.1	0.0515	8.46	0.0322	<LOW>
164	3.92	0.198	0.0561	0.554	105	0.0266	44.9	5.32	92	0.17	15.6	0.0322	<LOW>
165	63.7	0.198	0.133	1.03	107	0.0266	44.9	5.32	71.1	0.105	27.1	0.0322	<LOW>
166	73.1	0.23	0.00855	1.98	109	0.342	68.6	3.43	101	0.252		0.0453	0.529
167	61.9	0.333	0.0594	2.34	170	0.301	45.2	3.43	144	0.202	3.95	0.0453	1.12
168	13.6	0.1	0.0897	2.16	156	0.194	68.6	3.43	131	0.252	9.24	0.0453	0.529
169	61.9	0.426	0.0897	2.13	139	0.342	139	3.43	39.9	0.202	14	0.0453	0.529
170	641	3.4	2.3	3.42	499	1.05	356	216	292	0.605	49500	0.581	4.68
171	660	3.09	1.95	3.58	459	1.03	289	214	221	0.482	47200	0.733	3.74

	X	Y	Z	AA	AB	AC	AD	AE	AF	AG	AH	AI	AJ
172	525	3.19	1.68	3.07	486	0.87	334	226	231	0.472	44500	0.517	4.09
173	29.5	0.1	0.0494	1.91	30.1	0.226	56.9	3.43	**39.9**	0.202	5.67	**0.0453**	1.72
174	**7.97**	**0.1**	**0.00855**	1.84	**30.1**	0.21	**45.2**	**3.43**	**39.9**	0.15	**3.95**	**0.0453**	**0.529**
175	50.9	**0.1**	**0.00855**	2.4	**30.1**	0.382	74.5	5.21	84.1	0.252	27.3	**0.0453**	1.97
176	191	0.595	0.0296	2.67	37.3	0.445	185	18.5	84.1	0.389	46.1	0.234	2.61
177	7.97	0.513	0.0694	1.98	**30.1**	0.315	68.6	**3.43**	156	0.228	23.1	0.0679	**0.529**
178													
179													
180													
181													
182													
183													
184													
185													
186													
187													
188													

	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT	AU	AV
1												
2												
3												
4 5	IP-10 pg/ml	KC/GRO ng/ml	Leptin ng/ml	LIF pg/ml	ymphotactir pg/ml	MCP-1/JE pg/ml	MCP-3 pg/ml	MCP-5 pg/ml	M-CSF ng/ml	MDC pg/ml	MIP-1a ng/ml	MIP-1b pg/ml
6	93.4	0.128	1.4	28.5	154	64.3	500	294	1.98	142	6.74	61.9
7	121	0.167	1.19	42.2	176	111	888	358	2.75	138	4.53	61.9
8	104	0.224	0.985	42.2	184	77	450	235	1.87	81.7	6.38	9.4
9	127	0.154	1.4	42.2	193	77.8	475	283	2.05	79	6.74	48.6
10	139	0.0734	1.46	42.2	228	70.3	377	230	2.95	148	6.74	22.7
11	104	0.261	1.35	49.3	124	91.2	528	265	1.98	154	6.74	35.6
12	174	0.189	0.97	28.5	193	75.3	522	321	2.56	92.3	4.96	61.9
13	82.5	0.0975	0.93	1.78	141	56.3	317	161	1.12	61.2	4.96	9.4
14	2740	14.4	0.778	85.9	587	3850	6910	2970	3.74	603	9.8	2870
15	2770	70.6	0.985	120	700	14700	7740	3710	5.42	520	10.5	4850
16	2110	3.51	0.682	63.7	537	3390	7510	2790	2.87	302	8.47	1070
17	2210	128	1.57	378	603	36200	7360	5100	4.11	466	10.3	9550
18	2640	56.9	0.458	132	537	8920	7230	4180	2.7	435	13.3	11100
19	1190	3.75	1.02	71	424	1320	4990	1920	3.91	423	9.14	654
20	479	2.03	0.989	42.2	246	463	2550	960	3.67	256	9.47	203
21	277	2.99	0.682	63.7	193	379	1980	748	3.98	251	7.79	188
22	1500	1.45	0.503	21.8	394	779	3830	1500	1.32	279	6.07	420
23	907	2.19	0.679	50.3	206	816	3900	999	3.08	373	4.85	316
24	208	1.41	0.728	31.4	139	218	1780	550	1.38	208	4.21	102
25	224	0.311	0.543	26.8	142	220	1320	465	1.18	154	4.02	93.3
26	239	0.904	0.571	43.1	148	252	1190	421	2.6	215	5.1	75.3
27	2750	2.43	0.551	59.9	275	**980**	**4650**	1410	2.5	356	5.1	509
28	1990	0.874	0.408	36.1	351	980	4410	1010	2.42	279	4.76	375
29	1070	2	0.649	29.1	263	**980**	4650	1560	1.51	320	6.18	471
30	374	15.1	1.04	43.1	110	4890	5390	1950	1.62	433	1.79	**11000**
31	257	22.5	5.73	31.2	79	4640	6010	1870	1.74	201	2.65	8460
32	192	10.8	2.36	25.5	57.2	4150	5810	2570	2.5	248	0.747	616
33	338	31.9	5.68	49.3	53.6	5320	6380	2330	1.5	194	2.79	8700
34	71.2	0.0954	2.14	31.2	269	112	412	306	2.6	12	0.747	191
35	39.6	**0.0335**	1.41	17.2	118	106	531	281	2.84	8.84	0.574	0.876
36	39.6	0.0759	1.33	37.1	194	83.5	311	158	2.35	7.61	0.483	42.3
37	26.4	**0.0335**	1.47	25.5	147	67.5	280	155	2.29	4.15	0.662	11.2
38	28	**0.0335**	1.31	**5.02**	86.4	51.3	174	109	2.39	3.08	0.291	**0.876**
39	57	0.0954			143	113	331	201				33.9
40	39.6	0.0556	1.01	31.2	181	67.5	313	189	2.87	7.61	0.574	91.8
41	23.2	**0.0335**	2.37	34.1	122	53.8	187	148	2.07	5.26	0.618	3.81
42	533	1:18	0.476	19.9	210	2400	5880	1780	2.26	21.1	0.389	235

	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT	AU	AV
43	542	35.3			210	12500	6470	2800				6100
44	740	**0.0335**	0.73	316	329	**12500**	21100	4910	3.43	884	2.99	9050
45	288	1.53	0.735	68.6	219	1280	3500	1730	2.8	673	1.07	191
46	69.4	0.963	0.644	25.5	71.6	432	1520	769	1.74	293	0.747	72.6
47	50	1.35	0.59	43.1	160	468	1450	740	2.57	330	0.662	72.6
48	351	0.404	0.466	75.3	118	791	2420	1330	1.06	429	1.22	78.9
49	23.2	0.0335	2.03	5.02	71.6	104	553	263	1.51	108	0.389	**0.876**
50	17.1	0.0449	1.94	25.5	57.2	68.3	328	164	1.7	155	0.662	**0.876**
51	17.1	0.0759	2.28	37.1	106	86.6	350	164	1.69	167	0.483	24.3
52	727	4.2	0.735	58.8	293	4010	8760	2440	3.52	475	1.07	772
53	201	4.1	0.982	62.1	168	2250	5730	1920	2.98	448	1.22	547
54	254	8.39	1.89	43.1	36.5	1850	3180	1440	2.19	465	0.831	807
55	264	7.43	0.529	25.5	189	3040	4240	2310	2.02	414	1.15	1190
56	695	6.31	1.21	82.1	236	3040	5720	2260	4.07	759	1.15	1080
57	137	0.969	0.549	26.5	223	887	3520	1150	2.58	316	0.747	78.9
58	338	0.974	0.701	31.2	160	819	3170	1160	2.48	415	0.913	176
59	205	0.811	1.04	68.6	185	801	2740	1040	2.91	392	0.993	162
60	76.6	1.92	0.807	31.2	126	620	2030	726	3.4	324	1.07	206
61	118	0.737	1.03	19.9	177	381	1600	572	2.63	248	1.07	36.8
62	451	3.6	0.969	60.5	124	1730	7290	797	5.78	452	0.196	317
63	430	3.54	1.07	27.1	118	1840	7840	809	6.01	435	0.261	348
64	415	1.58	0.811	55	182	1430	5980	775	4.52	399	0.351	240
65	382	1.58	0.739	32.7	156	1340		856	4.74	402	0.322	240
66	320	2.03	0.989	43.9	291	1650	6050	789	6.08	323	0.357	250
67	283	2.13	0.999	49.5	256	1630		812	6.28	328	0.236	256
68	397	2.42	0.77	49.5	308	2550	9740	1080	6.17	385	0.261	411
69	385	2.41	0.687	27.1	272	2470	11000	1060	6.21	370	0.322	391
70	369	178	2.11	188	153	20400	37600	1660	3.81	287	17.4	33500
71	340	198	2.09	216	182	20600	38300	1620	3.96	279	19	43900
72	635	228	1.43	1230	160	23400	27400	1340	6.1	404	13.5	35500
73	658	227	1.51	1520	160	20500	26900	1340	6.13	489	13.8	37000
74	471	67.7	1.28	250	150	14600	26500	1490	4.39	446	1.15	8370
75	578	62.7	1.17	255	163	11000	22600	1640	4.56	410	1.07	7610
76	778	74.5	1.91	1150	346	11500	21700	1580	7.06	1120	1.15	6310
77	888	87.1	1.84	1090	324	11900	23400	1640	7.08	1150	1.2	6790
78	106	0.103	0.435	**3.53**	124	144	539	166	4.17	169	0.183	36.3
79	102	0.0564	0.397	**3.53**	105	131	542	170	4.34	174	0.169	25.7
80	189	0.544	0.77	**3.53**	40.4	850	4540	823	2.29	254	0.169	181
81	186	0.593	0.78	**3.53**	34	793		787	2.08	251	0.169	161
82	179	3.48	1.31	27.1	137	1840	7360	725	4.77	275	0.249	348
83	176	3.57	1.38	21.3	163	1840		708	5.09	305	0.196	315
84	183	0.947	0.515	52.2	234	730	3410	555	5.09	313	0.249	117
85	154	0.869	0.635	38.3	208	618		531	5.22	310	0.261	130

	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT	AU	AV
86	145	1	0.76	9.63	118	1050	7520	797	3.33	296	0.183	149
87	156	1.09	0.729	15.5	118	1070		873	3.29	287	0.169	149
88	145	0.713	0.692	9.63	85.7	932	6350	628	3.41	254	0.236	121
89	159	0.781	0.677	9.63	105	1010		685	3.68	260	0.236	114
90	98.7	2.19	0.667	35.5	46.9	806	4600	546	3.07	231	0.236	185
91	91.2	2.16	0.583	21.3	72.8	809		517	2.98	206	0.183	167
92	528	2.22	0.499	12.6	240	1150	5930	706	3.47	224	0.118	209
93	459	1.79	0.551	3.53	182	1170		596	3.37	211	0.183	152
94	71.9	0.781	0.551	**3.53**	131	299	1960	394	3.12	173	0.196	66.2
95	55.7	0.593	0.562	21.3	59.8	304		387	3.07	183	0.155	59.7
96	128	0.577	0.477	24.2	131	479	3510	548	3.55	268	0.223	98.4
97	83.6	0.51	0.53	27.1	144	437		508	3.46	273	0.249	66.2
98	277	0.475	0.277	12.6	69.5	739	5050	592	2.97	286	0.155	141
99	238	0.56	0.327	15.5	72.8	799		587	2.89	236	0.183	108
100	63.9	0.766	0.614	15.5	59.8	469	2620	390	3.24	171	0.141	79.2
101	55.7	0.642	0.625	9.63	40.4	463		357	2.92	164	0.169	43.1
102	346	68	5.97	456	237	14400	17400	1410	5.33	418	47.8	95600
103	337	77.3	5.63	426	169	16600	19200	1280	5.07	400	45.5	147000
104	344	68.8	5.67	446	195	15300	18400	1320	5.28	416	48.9	94100
105	349	82.9	6.07	406	211	16500	19500	1300	5.28	427	46.7	134000
106	397	67.8	6.01	466	246	15100	16700	1400	5.63	427	48	96400
107	346	74.3	5.92	419	295	17300		1340	5.31	426	46.2	
108	361	67.7	5.91	454	253	15900	18400	1300	5.32	426	45.8	93500
109	334		5.68	391	240			1330	5.41	404	44.5	
110	396	71.9	6.51	496	285	14700	17700	1380	5.57	507	53.4	92300
111	329		6.1	479	285			1390	5.75	454	49.6	
112	253	52.1	3.14	265	189	15000	12400	1210	4.97	479	17	81200
113	219		3.11	285	189			1130	5.02	464	17	
114	267	56.1	3.39	280	185	16300	13700	1260	5.24	522	17.9	89300
115	261	58.2	3.24	341	169	18800		1260	5.1	491	18.6	
116	209	56.5	2.91	280	182	15600	13200	1110	4.74	514	18.3	83600
117	212		2.99	296	131			1070	4.98	446	16.1	
118	242	55.4	3.08	270	179	15400	13800	1180	5.05	464	17.1	86100
119	209		3.01	326	105			1120	4.81	478	17.4	
120	219	82.5	2.76	252	124	23500	18000	1090	4.81	441	18.1	125000
121	199	72.3	2.52	229	92.1	21400	18500	1040	4.67	413	16.8	144000
122	27.7	**0.137**	0.83	**7.3**	105	55.2	344	42	4.65	115	0.177	40.2
123	54.9	**0.137**	0.236	**7.3**	105	121	615	112	4.71	102	**0.0283**	20.3
124	27.7	**0.137**	1.03	**7.3**	147	61.6	340	87.8	4.63	64.5	**0.0283**	22.7
125	32.5	**0.137**	0.876	**7.3**	94.7	70.1	352	108	4.79	84.3	**0.0283**	**4.99**
126	20.3	**0.137**	0.368	**7.3**	94.7	68	352	67.8	4.21	108	**0.0283**	27.7
127	22.8	**0.137**	0.706	**7.3**	89.3	68	309	67.8	3.67	96	**0.0283**	**4.99**
128	59.2	**0.137**	0.417	**7.3**	195	61.6	260	42	4.16	115	**0.0283**	25.2

	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT	AU	AV
129	37.1	0.137	0.563	7.3	147	61.6	344	94.6	4.79	104	0.0283	15.3
130	76.4	0.896	0.318	7.3	186	398	3250	519	4.96	183	0.0283	70.9
131	106	1.11	0.449	7.3	195	493	3940	486	4.79	192	0.0283	83.8
132	82.8	1.54	0.121	7.3	137	513	4190	558	5.37	227	0.177	78.6
133	216	2.95	0.384	7.3	256	715	4620	581	5.2	206	0.0283	99.3
134	216	1.38	1.05	7.3	242	640	6180	581	5.18	332	0.0283	122
135	178	0.989	0.17	7.3	142	485	4740	510	4.38	279	0.0283	76
136	84.9	1.87	0.351	95.3	166	550	4870	540	4.57	231	0.104	102
137	192	2.1	0.368	7.3	195	832	5240	604	4.65	203	0.0283	260
138	584	129	3.28	640	322	25600	39100	1660	5.37	624	3.95	17200
139	561	140	0.968	613	322	19100	48600	1880	7.23	796	1.46	10600
140	316	31.9	2.93	631	269	7650	11000	803	5.2	376	49.4	152000
141	532	109	1.02	850	287	21800	49200	1420	6.9	513	2.5	15700
142	231	4.73	2.19	121	94.7	1350	3070	598	4.49	149	0.531	16400
143	446	52.6	0.482	534	223	22000	27700	1300	6.6	406	1.28	10400
144	470	29.6	0.285	442	242	18500	31000	1510	4.9	689	0.489	5010
145	616	41.9	1.76	528	481	9770	11900	976	6.71	521	3.15	47200
146	216	0.564	0.153	7.3	233	997	8720	871	5.81	351	0.0283	188
147	379	1.11	0.409	7.3	278	644	6580	652	4.87	388	0.0283	203
148	122	0.137	0.236	7.3	205	489	5120	519	5.2	206	0.0283	70.9
149	224	0.488	0.277	7.3	233	567	3940	641	3.61	294	0.0283	112
150	174	0.684	0.587	7.3	205	264	1290	450	5.22	294	0.0283	76
151	59.2	1.44	0.466	7.3	171	302	1940	324	4.54	145	0.104	45.3
152	50.5	1.5	0.137	7.3	147	307	2900	334	4.76	156	0.0283	35.2
153	67.9	0.137	0.401	7.3	166	270	1940	298	3.94	162	0.0283	45.3
154	403	75.8	5.68	625	313	16800	24400	1400	5.59	564	43.1	131000
155	382	78.8	5.53	637	313	17400	23400	1330	5.64	502	41.6	118000
156	377	74.4	5.68	649	352	15300	21500	1320	5.75	505	40.6	104000
157	349	63	4.84	558	300	14900	19700	1170	5.01	462	36.4	106000
158	335	70.8	5.22	631	309	15400	21500	1160	5.92	459	37.8	126000
159	286	64.3	4.7	558	223	13400	19000	1020	5.2	430	36.6	103000
160	20.3	0.137	2.48	34.1	8.06	33.8	75	24	5.61	104	0.0283	4.99
161	41.6	0.137	2.19	7.3	72.5	32.6	61.9	32.8	5.09	92.1	0.0283	10.4
162	20.3	0.137	2.35	43.4	23.2	30.2	67.2	15.6	5.31	119	0.0283	15.3
163	32.5	0.137	2.43	34.1	8.06	35	61.9	24	6.14	108	0.0283	22.7
164	39.3	0.137	2.33	52.1	89.3	41.9	77.7	35.8	5.61	109	0.0283	35.2
165	41.6	0.137	2.27	84	121	44.1	72.4	74.4	5.15	111	0.0283	17.8
166	74.4	0.0529	2.88	86.2	44.5	52.4	86.8	55.4	7.72	171	0.172	34.4
167	83.6	0.185	2.81	52.9	91.9	48	65.5	48.5	7.11	176	0.191	77.9
168	60.7	0.0807	2.85	65.5	75.8	49.1	86.8	27.2	6.17	208	0.172	25
169	56.2	0.108	2.68	102	29	31.3	62.9	41.5	6.23	168	0.21	15.6
170	605	79.5	6.5	801	490	17800	21700	1480	8.76	766	44.5	133000
171	500	78.4	6.08	752	397	16800	21100	1450	8.07	732	41.7	131000

	AK	AL	AM	AN	AO	AP	AQ	AR	AS	AT	AU	AV
172	531	73.1	5.76	702	387	17600	20000	1400	8.15	671	40.3	111000
173	69.9	0.0529	1.13	61.3	133	63.3	318	82.5	5.08	236	0.162	44
174	24.5	**0.0529**	1.31	86	25.1	55.7	216	75.8	5.47	125	0.108	39.2
175	156	0.241	1.52	94.3	168	187	708	152	5.24	282	0.237	97.4
176	134	0.599	0.685	181	285	437	870	250	5.71	298	0.313	198
177	74.4	0.135	0.465	52.9	87.8	197	419	99.2	6.84	152	0.172	48.8
178												
179												
180												
181												
182												
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184												
185												
186												
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188												

	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
1												
2												
3												
4	MIP-1g	MIP-2	MIP-3b	Myoglobin	OSM	RANTES	SCF	SGOT	TIMP-1	Tissue Factor	TNFa	TPO
5	ng/ml	pg/ml	ng/ml	ng/ml	ng/ml	pg/ml	pg/ml	ug/ml	ng/ml	ng/ml	ng/ml	ng/ml
6		29.8	0.193	13.9	0.0616	61.2	21.1	0.733	1.8	6	0.0358	6.67
7		32.9	0.193	13.8	0.0616	93.3	21.1	1.24	2.62	5.6	0.0591	6.88
8		17.7	0.267	97	0.0616	54	21.1	1.42	1.57	8.32	0.0221	8.18
9		29.8	0.243	189	0.0616	90.8	21.1	1.99	2.53	8.64	0.033	8.24
10		29.8	0.243	3.28	0.0616	51.6	21.1	0.373	3.18	5.2	0.033	6.53
11		36	0.34	51	0.0616	90.8	21.1	2.92	3.78	8.4	0.0443	7.37
12		42.3	0.267	16.8	0.0616	49.3	21.1	1.24	1.95	6.16	0.0386	7.77
13		14.7	0.0942	3.18	0.0616	42.3	21.1	10.4	1.47	4.64	0.0275	5.46
14		1140	0.614	24.5	0.372	849	302	0.568	38.8	7.52	0.523	10.9
15		4590	0.941	52.4	0.61	1180	528	0.167	63	9	0.875	13.8
16		298	0.434	30.8	0.27	726	185	0.38	31.4	7.6	0.366	10.8
17		17400	1.51	**189**	0.849	1790	954	0.983	50.1	15.5	1.27	12.9
18		14300	1.02	32.1	0.74	1900	682	4.32	33.8	9.36	1.24	12.5
19		240	0.434	47	0.155	474	97.3	0.568	14.5	8.24	0.184	9.36
20		111	0.387	18	0.0616	272	21.1	0.88	11.9	7.4	0.124	9.36
21		164	0.387	23.6	0.0661	181	43.5	0.983	9.99	7.2	0.107	8.51
22		74.8	0.291	123	0.15	552	26.4	9.04	10.3	8.64	0.163	7.91
23		154	0.472	20.3	0.142	330	172	1.12	12.4	5.62	0.151	6.33
24		71.3	0.383	47.8	0.0569	186	69.7	4.74	4.53	5.85	0.0667	5.03
25		56.5	0.294	67.1	0.0569	144	69.7	7.14	3.93	5.97	0.071	5.2
26		67.6	0.383	7.31	0.0343	118	69.7	0.488	6.26	4.55	0.0583	5.36
27		143	0.472	56	0.182	443	227	0.76	11.6	5.92	0.208	7.67
28		83.5	0.472	16.4	0.138	337	129	0.496	8.49	5.26	0.151	7.26
29		116	0.668	47.4	0.175	454	166	3.36	8.23	7.4	0.176	7.9
30		1520	0.247	84.9	0.0979	288	117	6.65	61	1.03	0.479	6.63
31		6230	0.284	302	0.0677	189	196	6.91	46.3	1.48	0.598	7.07
32		296	0.393	**302**	0.0979	80.3	205	4.66	37.8	1.21	0.263	7.71
33		9140	0.321	131	0.075	223	134	6.18	51.8	1.14	0.585	7.42
34		18.6	0.0252	79.2	0.0677	83	214	**0.932**	3.4	1.44	0.207	4.45
35		9.83	**0.0252**	56.4	0.0261	53.3	117	4.17	2.45	0.806	0.0369	4.05
36		10.8	0.0637	**302**	0.0207	47.8	85.4	**0.932**	2.26	1.99	0.0369	5.14
37		12.8	0.0252	**302**	0.0207	53.3	81.6	**0.932**	2.74	2.04	**0.00622**	4.52
38		4.72	0.0637	10.2	**0.00257**	53.3	70.6	2.88	3.03	0.718	0.0412	3.26
39		10.8			0.0261	75	134		3.9		0.0636	
40		12.1	0.1	75.4	0.0605	102	101	**0.932**	2.05	1.23	0.0501	3.97
41		4.28	0.0637	25.1	0.00641	36.9	57.1	5.05	1.61	0.939	0.0281	4.21
42		108	0.0452	98.2	0.0261	80.3	77.9	2.43	19.5	1.35	0.0728	5.37

	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
43		**9140**			0.118	275	335		99.7		0.757	
44		**9140**	0.893	189	0.225	461	408	1.65	**261**	3.34	0.93	12.5
45		105	0.357	155	0.0156	164	125	**0.932**	10.5	2.41	0.107	8.05
46		42.2	0.321	56.5	0.00257	125	85.4	6.79	7.63	2.22	0.0919	6.63
47		107	0.173	77.3	0.0132	112	134	3.28	8.08	1.76	0.0456	7.07
48		29.6	0.21	**302**	0.0108	96.4	57.1	4.62	7.78	2.66	0.0456	7.14
49		4.72	0.0252	136	**0.00257**	56	42.9	5.66	1.81	1.74	**0.00622**	5.44
50		4.06	0.173	**302**	**0.00257**	42.3	37.4	3.17	1.31	2.34	**0.00622**	7.63
51		6.97	0.0252	**302**	0.00641	42.3	70.6	**0.932**	1.63	2.95	0.00622	6.92
52		271	0.393	123	0.122	184	233	2.64	30.7	1.81	0.298	8.61
53		288	0.357	183	0.0359	112	93.1	2.31	17	2.31	0.102	9.22
54		373	0.357	140	0.0412	104	57.1	3.47	24.2	1.71	0.112	8.95
55		466	0.357	137	0.0261	143	109	6.57	13.4	2.41	0.153	10.1
56		594	0.429	49.7	0.0318	96.4	77.9	**0.932**	17.3	1.67	0.122	11.6
57		43.9	0.173	**302**	0.0108	85.7	70.6	4.32	16	2.18	0.0728	7.21
58		90.6	0.229	146	**0.00257**	56	42.9	5.13	12.1	2.04	0.0281	7.07
59		97.6	0.284	86.8	0.0384	120	142	3.84	11.3	1.85	0.0728	7.63
60		287	0.0637	**302**	0.0318	69.6	160	**0.932**	13.1	2.77	0.0682	8.33
61		49.2	0.173	32.1	0.0261	85.7	77.9	**0.932**	12.7	1.76	0.0369	7.92
62	39.3	353	0.189	20.7	0.0959	29.6	95.8	2.7	22.1	1.27	0.137	11.4
63	46.3	344	0.399	42.1	0.11	31.7	51.8	2.82	24.4	1.72	0.137	12.6
64	44	152	0.455	18.9	**0.0648**	31.7	87.8	4.4	14.6	1.52	0.0983	10.7
65	46.5	147	0.455		**0.0648**	23.8	63.9	3.58	14.7	1.3	**0.0365**	10.3
66	34.1	189	0.371	22.5	0.218	39.8	160	0.151	19.5	2.11	0.27	12.6
67	41.6	202	0.342		0.117	37.8	192	0.211	22.1	1.89	0.258	11.3
68	39.3	215	0.342	21.3	0.165	68.5	233	1.2	22.5	1.72	0.329	12.2
69	46.8	212	0.221	51.7	0.271	55.8	160	0.812	20.9	1.66	0.234	13.7
70	68.2	41000	0.221	41.1	0.323	164	321	8.39	300	2.67	1.2	9.98
71	88.8	48500	0.157	75	0.349	172	321	7.23	326	3.09	1.13	11
72	130	61700	0.455	606	0.455	180	382	4.11	505	3.57	1.73	10.6
73	147	72700	0.482	780	0.508	191	378	4.24	511	4.02	1.71	11.7
74	167	12200	0.482	5750	0.297	131	229	7.99	235	2.98	0.786	12.3
75	204	9050	0.427	6060	0.349	123	241	9.4	201	2.45	1.01	11.8
76	149	14100	2.47	235	0.455	134	374	**0.151**	148	3.68	0.943	19
77	214	15700	2.55	387	0.494	143	442	**0.151**	182	3.46	1.13	18.4
78	24.8	18.9	0.107	75.1	**0.0648**	**4.71**	39.6	6.3	5.71	0.984	**0.0365**	6.33
79	28.1	18.2	0.124	74.2	**0.0648**	**4.71**	39.6	7.75	5.94	0.814	**0.0365**	6.33
80	37.6	53.1	0.221	10.5	**0.0648**	26.2	**12.2**	16	6.29	1.21	**0.0365**	7.52
81	42.5	42.9	0.157		**0.0648**	4.71	**12.2**	17.3	5.86	0.671	**0.0365**	6.33
82	32.3	256	0.221	36.3	0.138	44.5	156	2.51	21.9	1.55	0.204	10.5
83	37.6	247	0.124		0.152	41.7	104	3.48	21.2	1.49	0.162	11.5
84	31.9	99.8	0.141	35.7	0.117	27.3	120	1	13.3	1.72	0.15	9.07
85	32.5	77.3	0.189		0.0959	33.8	164	0.917	12	1.55	0.131	11.3

	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
86	39.4	42.1	0.0732	161	**0.0648**	29.6	43.7	16.6	8.33	2.06	**0.0365**	9.57
87		33.7	0.157		0.0648	41.7	87.8	18.2	8.61	2.03	0.0365	10.1
88	31.8	49.7	0.157	63	**0.0648**	25	12.2	13.4	6.73	1.32	**0.0365**	8.3
89	39.4	45.5	0.221		**0.0648**	29.6	12.2	12.7	6.65	1.58	**0.0365**	9.81
90	35	134	0.124	48.3	**0.0648**	35.9	**12.2**	18.4	9.26	2.11	**0.0365**	9.65
91	42.6	129	0.107		**0.0648**	35.9	12.2	20.1	8.99	1.83	**0.0365**	8.3
92	31.5	123	0.157	63	0.0809	50.7	55.9	18.9	11.6	2.06	0.112	11.3
93	41.9	87.9	0.157		**0.0648**	33.8	55.9	19.7	10.2	1.55	0.0841	9.98
94	32	65.5	0.124	42.3	0.0809	37.8	71.9	15.4	8	1.49	0.162	10.9
95	41.6	54.2	0.0905		**0.0648**	26.2	31.2	16.1	7.64	1.27	**0.0365**	9.15
96	31.5	67.3	0.221	108	0.0648	41.7	63.9	12.2	7.47	2.06	0.131	9.65
97	44.4	36.7	0.342		**0.0648**	27.3	47.8	12.9	6.79	2.14	**0.0365**	10.5
98	34.1	45.9	0.221	42.9	**0.0648**	31.7	71.9	16.3	6.86	1.49	**0.0365**	8.65
99		28.3	0.221		**0.0648**	45.4	79.9	19.2	6	1.78	**0.0365**	7.78
100	33.4	83.5	0.0905	87.5	**0.0648**	17.1	12.2	18.3	8.31	1.32	**0.0365**	8.98
101	44.5	61	0.107		**0.0648**	4.71	**12.2**	20	7.9	1.1	**0.0365**	9.32
102	57	29100	0.637	132	0.494	183	261	1.03	410	4.85	2	14.7
103	78	39200	0.599	204	0.402	164	241	1.01	476	4.8	1.73	13.1
104	59.1	31800	0.561	118	0.508	175	293	0.427	426	4.52	1.84	14.4
105	73	39900	0.509	116	0.376	172	329	1.29	486	3.93	1.84	15.8
106	61.6	31700	0.455	150	0.468	197	386	0.359	462	5.52	2.16	16.4
107	60	36000	0.455	164	0.547	187	313	**0.151**	517	4.68	2.02	14.5
108	62	31000	0.685	128	0.508	173	305	0.388	448	4.88	1.83	17.4
109	70.2		0.709		0.455	172	418	0.677		4.43	1.96	14.1
110	58.6	28800	0.637	122	0.508	201	362	**0.151**	406	5.19	2.16	16.7
111			0.637		0.561	205	321	0.281		5.3	2.06	16.1
112	51.8	17300	0.535	59.5	0.455	157	245	1.97	473	3.57	1.46	13.5
113	66.9	23700	0.586		0.362	137	224	1.93		3.21	1.31	14.1
114	54.1	20100	0.586	72.2	0.362	149	241	**0.151**	474	3.4	1.41	12.8
115	52.8	21800	0.482		0.428	147	265	**0.151**		3.51	1.37	13.1
116	54.4	19500	0.441	54.8	0.336	137	265	2.24	468	3.4	1.26	13.4
117		26400	0.455		0.284	131	229	1.81		3.09	1.22	13.7
118	54	19000	0.509	87	0.336	130	233	**0.151**	487	2.9	1.17	13.1
119	66.5		0.509		0.343	130	208	2.09		2.84	1.18	12.6
120	98	28700	0.535	174	0.218	141	200	2.53	618	3.29	1.01	13.2
121	73	24700	0.356		0.257	136	180	2.95	604	3.12	1.06	12.3
122	16.4	**6**	**0.0362**	82	**0.0104**	**8.44**	34	11.6	2.35	4.01	**0.054**	6.86
123	14.1	**6**	**0.0362**	180	**0.0104**	**8.44**	64.6	12	1.67	**0.00656**	**0.054**	2.84
124	13.5	7.93	**0.0362**	102	**0.0104**	**8.44**	84.7	10.6	1.28	**0.00656**	**0.054**	2.11
125	14.7	6	**0.0362**	108	**0.0104**	**8.44**	84.7	12.1	1.42	**0.00656**	**0.054**	1.92
126	13.8	**6**	**0.0362**	17.7	**0.0104**	**8.44**	23.4	10.8	1.1	0.924	**0.054**	5.41
127	14.3	**6**	0.332	121	**0.0104**	**8.44**	**3.33**	9.12	0.997	**0.00656**	**0.054**	1.92
128	14.2	**6**	**0.0362**	28.6	0.0692	16.8	64.6	10.4	1.45	**0.00656**	0.0636	1.51

	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
129	16.3	12.5	**0.0362**	80.1	**0.0104**	8.44	64.6	11.8	1.71	0.618	**0.054**	3.86
130	32.9	58	0.0362	21.6	**0.0104**	37.8	84.7	11.3	11	**0.00656**	0.195	2.84
131	24.1	63.9	0.0362	129	0.0104	37.8	94.8	9.55	9.91	0.3	0.166	5.11
132	23.1	59.4	**0.0362**	34.8	**0.0104**	**8.44**	44.3	10.5	9.93	0.514	0.122	7
133	27.3	91.1	0.0362	109	0.0468	8.44	120	10.5	10.6	0.188	0.181	4.81
134	31.1	71.1	0.407	72.3	0.101	8.44	105	10.4	9.36	0.00656	0.152	5.41
135	31.8	46.5	0.147	37.8	**0.0104**	**8.44**	74.7	10.1	8.12	**0.00656**	0.0636	4.81
136	29.8	53.4	0.214	139	**0.0104**	8.44	**3.33**	12.6	10.8	**0.00656**	**0.054**	4.18
137	33.5	89.8	**0.0362**	123	**0.0104**	8.44	54.4	12.2	10.9	2.46	0.0727	4.81
138	84.6	10800	0.89	89.2	0.456	194	295	1.51	204	3.2	1.58	8.76
139	144	39900	2.47	776	0.401	174	363	4.64	366	3.2	1.87	11.7
140	47.2	22900	0.407	78.9	0.651	156	245	1.67	457	2.37	2.39	7.82
141	131	33200	2.02	116	0.365	156	334	-3.27	457	2.55	1.69	8.89
142	46.5	1140	0.332	99.2	0.0231	62.3	105	14.4	84.6	0.772	0.231	5.41
143	92.8	6990	1.22	272	0.252	88.4	270	3.93	80.6	2.6	0.702	9.67
144	84.9	1210	1.02	338	0.242	119	245	7.76	203	1.94	0.676	6.72
145	60.2	5510	1.38	853	0.51	183	402	1.57	416	5.65	1.42	9.8
146	30.9	63.9	0.183	391	**0.0104**	35.8	74.7	8.49	9.06	0.188	0.129	4.65
147	39.2	65.7	0.11	20.2	**0.0104**	51.6	155	6.79	19	**0.00656**	0.252	3.86
148	24.6	15.1	**0.0362**	123	**0.0104**	31.8	39.2	**11.1**	7.46	**0.00656**	**0.054**	2.84
149	30.8	37	0.0362	242	**0.0104**	22.5	74.7	10.8	9.12	**0.00656**	**0.054**	2.11
160	31	36	**0.0362**	16.1	**0.0104**	16.8	74.7	10.7	8.83	**0.00656**	0.054	3.53
151	26	55.7	0.0362	26.1	0.0231	**8.44**	44.3	9.82	7.59	**0.00656**	0.054	5.11
152	31	47.4	**0.0362**	35.1	**0.0104**	35.8	64.6	11.1	9.82	0.3	**0.054**	3.19
153	24.6	17.4	0.11	53.2	**0.0104**	**8.44**	54.4	12	6.38	0.0713	**0.054**	4.18
154	66.6	41000	0.825	586	0.599	171	314	0.894	452	3.29	2.01	9.92
155	65	39200	0.553	440	0.537	182	334	1.76	486	2.83	2.1	9.02
156	60.4	37400	0.922	484	0.581	191	402	**0.894**	403	3.38	2.09	8.89
157	55.4	31400	0.481	412	0.642	180	324	2.55	418	2.65	1.96	8.23
158	62.8	38600	0.758	449	0.438	169	354	2.61	423	3.15	1.74	9.54
159	57.9	32100	0.953	451	0.519	158	285	2.81	390	3.29	1.57	8.23
160	17.7	6	0.0362	80.4	**0.0104**	**8.44**	23.4	15.9	1.2	**0.00656**	**0.054**	0.843
161	15.5	7.93	0.11	88	**0.0104**	**8.44**	34	15.6	1.03	0.00656	**0.054**	0.843
162	16.5	**6**	0.11	83.4	**0.0104**	**8.44**	11.8	15.5	0.938	0.721	**0.054**	3.19
163	17.9	16.8	**0.0362**	89.2	**0.0104**	**8.44**	**3.33**	15.2	1.09	0.408	**0.054**	3.86
164	15.5	29.1	0.11	87.8	**0.0104**	**8.44**	3.33	15.2	0.95	0.0713	**0.054**	2.84
165	14.4	23.4	0.553	89.5	**0.0104**	**8.44**	54.4	15.4	0.95	0.823	**0.054**	3.02
166	19	4.81	0.326	67.3	0.0516	34.2	14.1	10.7	1.25	2.01	**0.0206**	9.06
167	19.6	4.16	0.474	63.5	0.142	37.9	33.7	10.8	1.11	2.07	0.0425	8.29
168	18.1	2.87	0.474	63.5	0.134	37.9	14.1	12	1.1	2.01	0.0206	8.18
169	19.2	4.16	0.543	58.8	0.0663	21.9	33.7	11.5	0.846	2.04	**0.0206**	8.4
170	84.1	39600	1.7	216	0.974	244	411	**1.43**	489	6.88	2.75	19.4
171	70.2	38000	1.5	188	0.883	213	401	**1.43**	454	5.57	2.36	15.3

	AW	AX	AY	AZ	BA	BB	BC	BD	BE	BF	BG	BH
172	68.5	32000	1.26	187	0.811	218	277	**1.43**	416	6.16	2.48	16.3
173	18.8	5.48	0.192	68	0.0959	12	30.3	4.61	2.39	1.5	0.0489	7.27
174	21.6	**2.87**	0.677	89.6	0.0442	14.8	**14.1**	13.9	1.47	1.75	**0.0206**	5.85
175	37.2	38.9	0.71	233	0.0367	17.3	26.9	5.09	5.1	2.91	0.10	10.3
176	29	93.4	0.677	278	0.221	32.2	95.4	1.43	5.57	2.59	0.0792	13.2
177	29.2	14.2	0.402	4.69	**0.0367**	**12**	40.8	11.8	2.07	1.43	**0.0206**	6.09
178												
179												
180												
181												
182												
183												
184												
185												
186												
187												
188												

	BI	BJ	BK
1			
2			
3			
4	VCAM-1	VEGF	vWF
5	ng/ml	pg/ml	ng/ml
6	<HIGH>	249	15.5
7	<HIGH>	313	13.6
8	<HIGH>	202	7.17
9	<HIGH>	297	14.8
10	<HIGH>	345	16.7
11	<HIGH>	329	14.2
12	<HIGH>	345	13.3
13	<HIGH>	202	3.96
14	<HIGH>	1040	18.6
15	<HIGH>	1540	29.1
16	<HIGH>	949	9.9
17	<HIGH>	2330	16.7
18	<HIGH>	1540	13
19	<HIGH>	676	22.3
20	<HIGH>	503	19.5
21	<HIGH>	440	19.8
22	<HIGH>	440	5.1
23	<HIGH>	370	18.6
24	<HIGH>	195	7.12
25	<HIGH>	153	5.71
26	<HIGH>	249	16.8
27	<HIGH>	459	18.8
28	<HIGH>	437	13.7
29	<HIGH>	392	7.12
30	<HIGH>	274	6.99
31	<HIGH>	213	13.4
32	<HIGH>	144	40.8
33	<HIGH>	240	11.4
34	<HIGH>	111	96.6
35	<HIGH>	58.4	76.5
36	<HIGH>	66.8	69.5
37	<HIGH>	68.9	79.2
38	<HIGH>	60.5	81.5
39		71.1	
40	<HIGH>	88.6	101
41	<HIGH>	54.4	69.5
42	<HIGH>	93	74.9

	BI	BJ	BK
43		384	
44	<HIGH>	301	96.6
45	<HIGH>	66.8	51.2
46	<HIGH>	46.9	22.9
47	<HIGH>	66.8	52
48	<HIGH>	15.6	32
49	<HIGH>	35.5	28.5
50	<HIGH>	35.5	18.7
51	<HIGH>	62.5	34.2
52	<HIGH>	155	81.1
53	<HIGH>	93	63.4
54	<HIGH>	97.4	62.6
55	<HIGH>	97.4	37.1
56	<HIGH>	115	86.9
57	<HIGH>	79.8	55
58	<HIGH>	58.4	55
59	<HIGH>	93	64.9
60	<HIGH>	97.4	85
61	<HIGH>	93	81.1
62	584	96.5	94.2
63	901	98.3	104
64	816	77.1	82.3
65		82.4	82.3
66	559	113	120
67		125	121
68	636	140	107
69	831	107	108
70	1020	599	8.24
71	1390	604	10.8
72	1470	1520	24.1
73	2050	1520	24.5
74	1360	185	20.2
75	1670	252	17.7
76	1250	492	241
77	1720	584	246
78	724	46.1	45.2
79		51.2	42.2
80	868	31.1	33.8
81		26.1	31.3
82	569	111	76.2
83		100	71.4
84	759	93	90.7
85		98.3	99.8

	BI	BJ	BK
86	762	36.1	25.4
87		52.9	26.2
88	768	54.6	30.5
89		49.5	27.9
90	629	27.8	27.1
91		24.4	22.8
92	704	75.4	21.1
93		34.4	22
94	650	44.5	33.8
95		31.1	28.8
96	760	51.2	28.8
97		47.8	27.9
98	764	17.6	22.8
99		42.8	24.9
100	656	27.8	24.1
101		21.1	26.2
102	848	1350	126
103	1300	1200	117
104	908	1340	127
105	1180	1310	145
106	865	1290	135
107		1280	127
108	940	1270	132
109		1270	124
110	828	1430	134
111		1190	132
112	948	800	116
113		873	111
114	992	961	140
115		963	125
116	918	860	123
117		829	112
118	952	895	125
119		876	111
120	2000	800	123
121		754	120
122	830	42.2	14.5
123	714	42.2	21.4
124	688	52	16.2
125	710	56.6	15.6
126	636	36.9	16.8
127	698	24.7	26
128	650	31.2	19.1

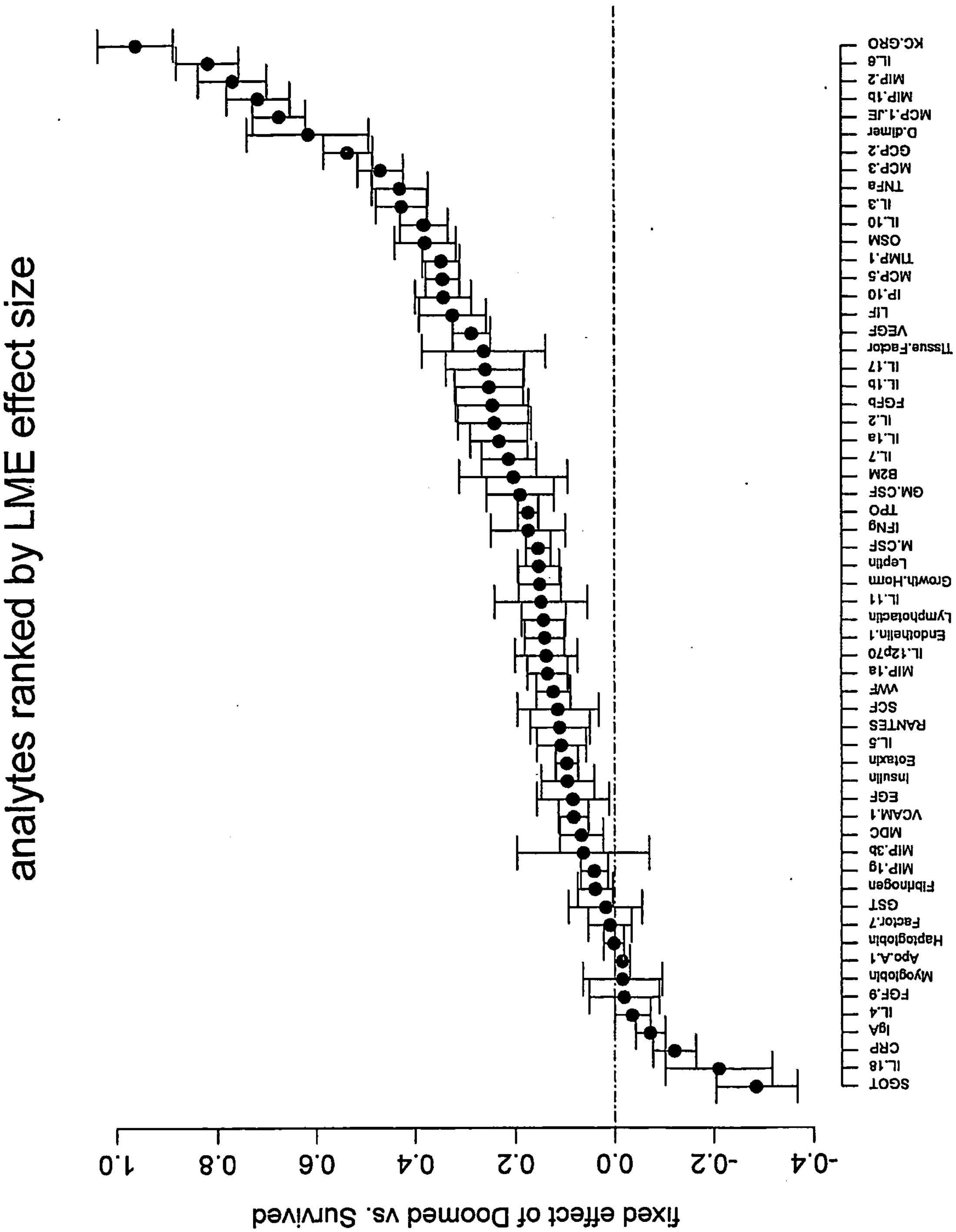
	BI	BJ	BK
129	671	56.6	20.2
130	840	82.9	17.9
131	972	82.9	15.6
132	866	52	24.8
133	911	70.2	23.7
134	936	49.6	29.5
135	940	61.3	24.8
136	844	36.9	27.7
137	714	82.9	30.6
138	1470	451	90.5
139	1510	397	86.6
140	1300	2420	67.4
141	1770	595	86.6
142	1160	189	17.9
143	1770	263	89.9
144	1590	394	76.4
145	1600	719	125
146	1050	78.8	17.9
147	1340	72.4	37.6
148	978	52	23.7
149	899	70.2	23.1
150	800	65.8	25.4
151	690	56.6	24.8
152	777	24.7	26
153	793	65.8	23.7
154	1270	1490	122
155	1220	1390	107
156	1150	1380	107
157	1160	1220	92.2
158	1110	1200	98.8
159	995	1150	93.3
160	1080	15.5	5.53
161	1030	42.2	8.83
162	1120	52	6.62
163	1130	15.5	5.53
164	1030	65.8	8.83
165	991	42.2	8.27
166	1610	50.8	11.8
167	1620	56.2	10.8
168	1380	27.2	9.83
169	1440	38.1	14.7
170	1900	1600	161
171	1700	1470	143

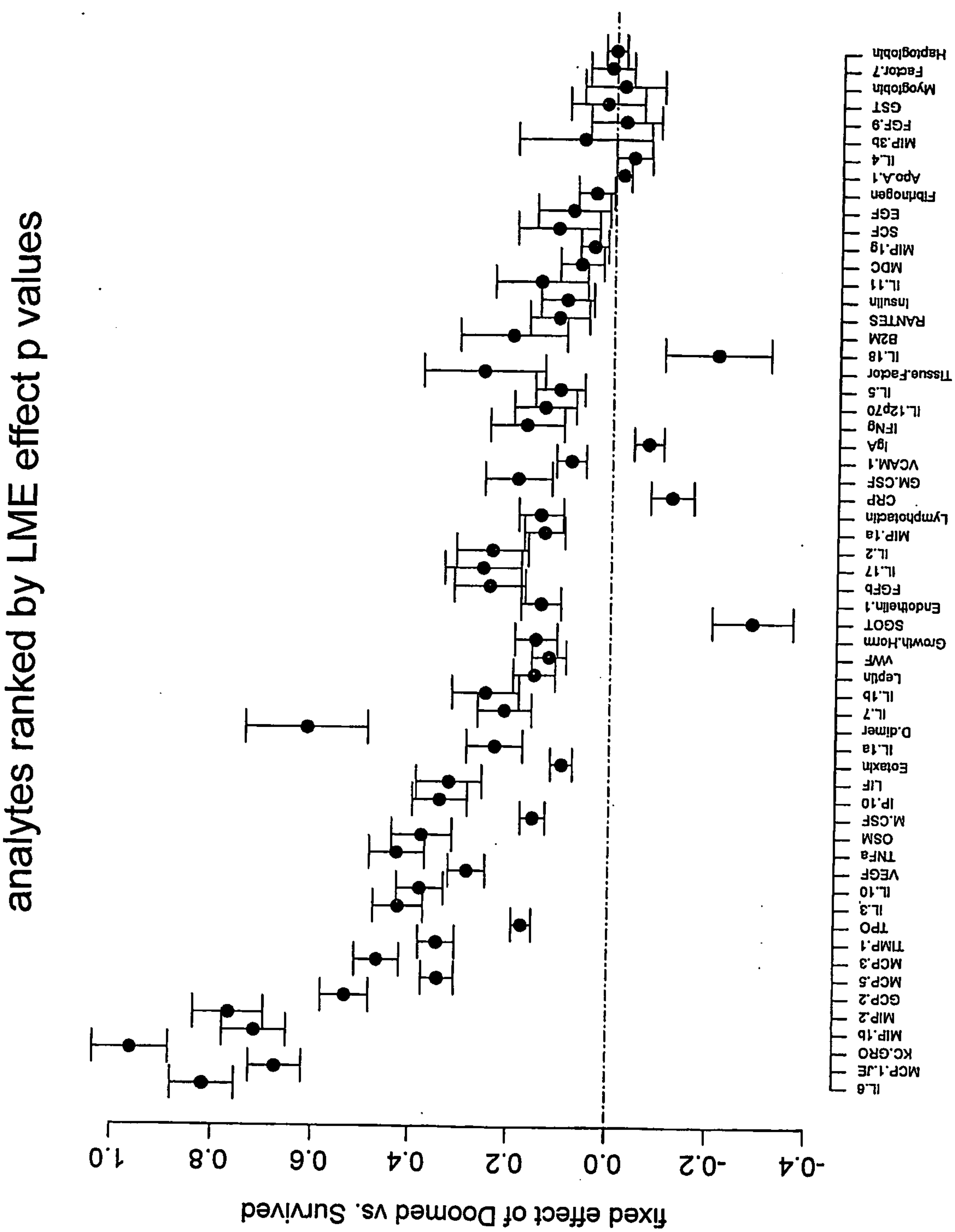
	BI	BJ	BK
172	1610	1520	165
173	1420	72.9	12.3
174	1530	38.1	19.7
175	1350	86	8.38
176	1730	101	13.7
177	1620	34.5	17.7
178			
179			
180			
181			
182			
183			
184			
185			
186			
187			
188			

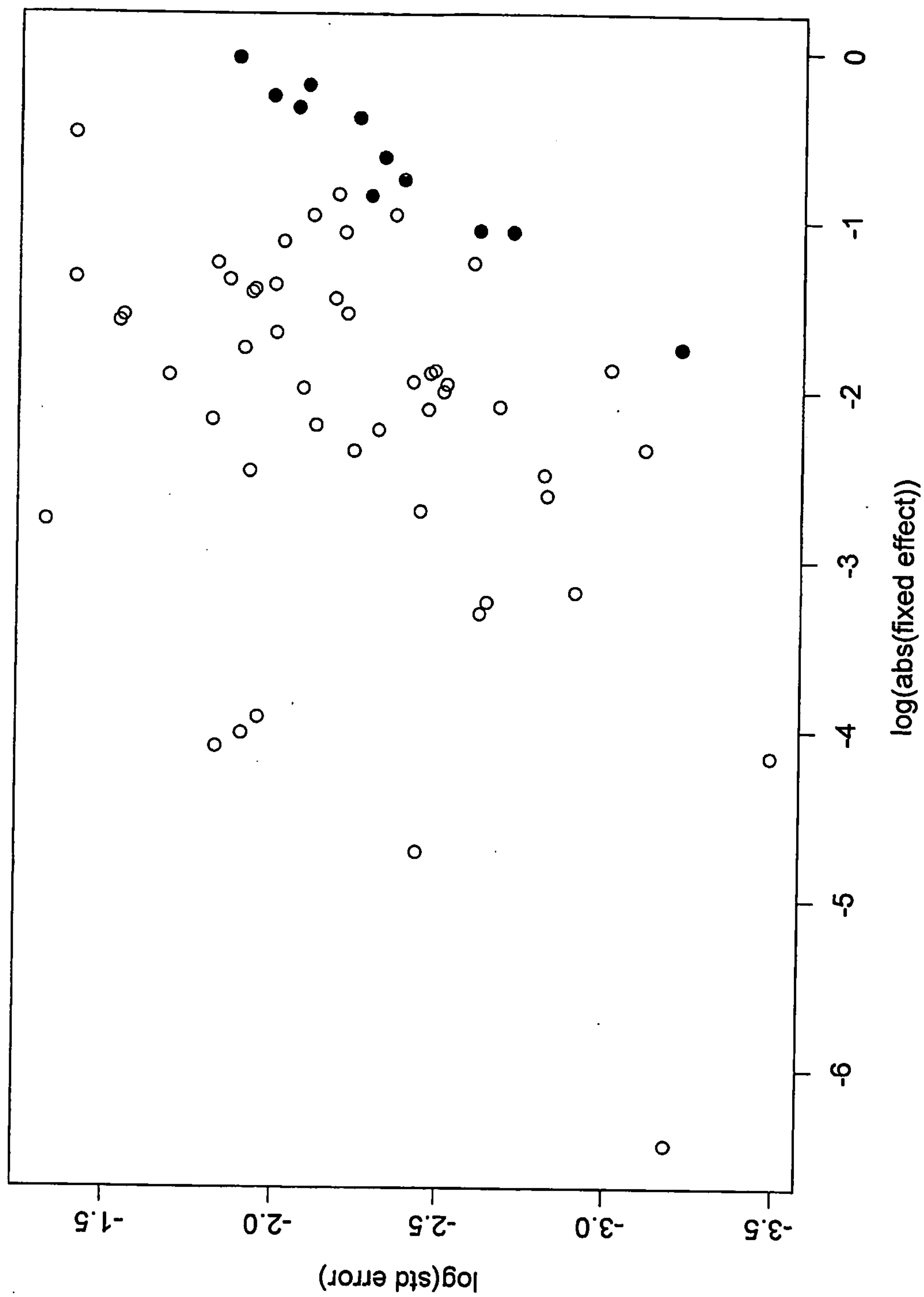
Appendix B

Analytes identified by linear mixed models using all data available

Treating experiments as random blocks


analytes ranked by LME effect size
KC.GRO
IL.6
MIP.2
MIP.1b
MCP.1.JE
D.dimer
GCP.2
MCP.3
TNFa
IL.3
IL.10
OSM
TIMP.1
MCP.5
IP.10
LIF
VEGF
Tissue.Factor
IL.17
IL.1b
FGFb
IL.2
IL.1a
IL.7
B2M
GM.CSF
TPO
IFNg
M.CSF
Leptin
Growth.Horm
IL.11
Lymphotactin
Endothelin.1
IL.12p70
MIP.1a
vWF
SCF
RANTES
IL.5
Eotaxin
Insulin
EGF
VCAM.1
MDC
MIP.3b
MIP.1g
Fibrinogen
GST
Factor.7
Haptoglobin
Apo.A.1
Myoglobin
FGF.9
IL.4
IgA
CRP
IL.18
SGOT
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
-0.4
fixed effect of Doomed vs. Survived


analytes ranked by LME effect p values
Haptoglobin
Factor.7
Myoglobin
GST
FGF.9
MIP.3b
IL.4
Apo.A.1
Fibrinogen
EGF
SCF
MIP.1g
MDC
IL.11
Insulin
RANTES
B2M
IL.18
Tissue.Factor
IL.5
IL.12p70
IFNg
IgA
VCAM.1
GM.CSF
CRP
Lymphotactin
MIP.1a
IL.2
IL.17
FGFb
Endothelin.1
SGOT
Growth.Horm
vWF
Leptin
IL.1b
IL.7
D.dimer
IL.1a
Eotaxin
LIF
IP.10
M.CSF
OSM
TNFa
VEGF
IL.10
IL.3
TPO
TIMP.1
MCP.3
MCP.5
GCP.2
MIP.2
MIP.1b
KC.GRO
MCP.1.JE
IL.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8
1.0
fixed effect of Doomed vs. Survived


log(abs(fixed effect))
0
-1
-2
-3
-4
-5
-6
log(std error)
-1.5
-2.0
-2.5
-3.0
-3.5

Performance validation

Based on p values

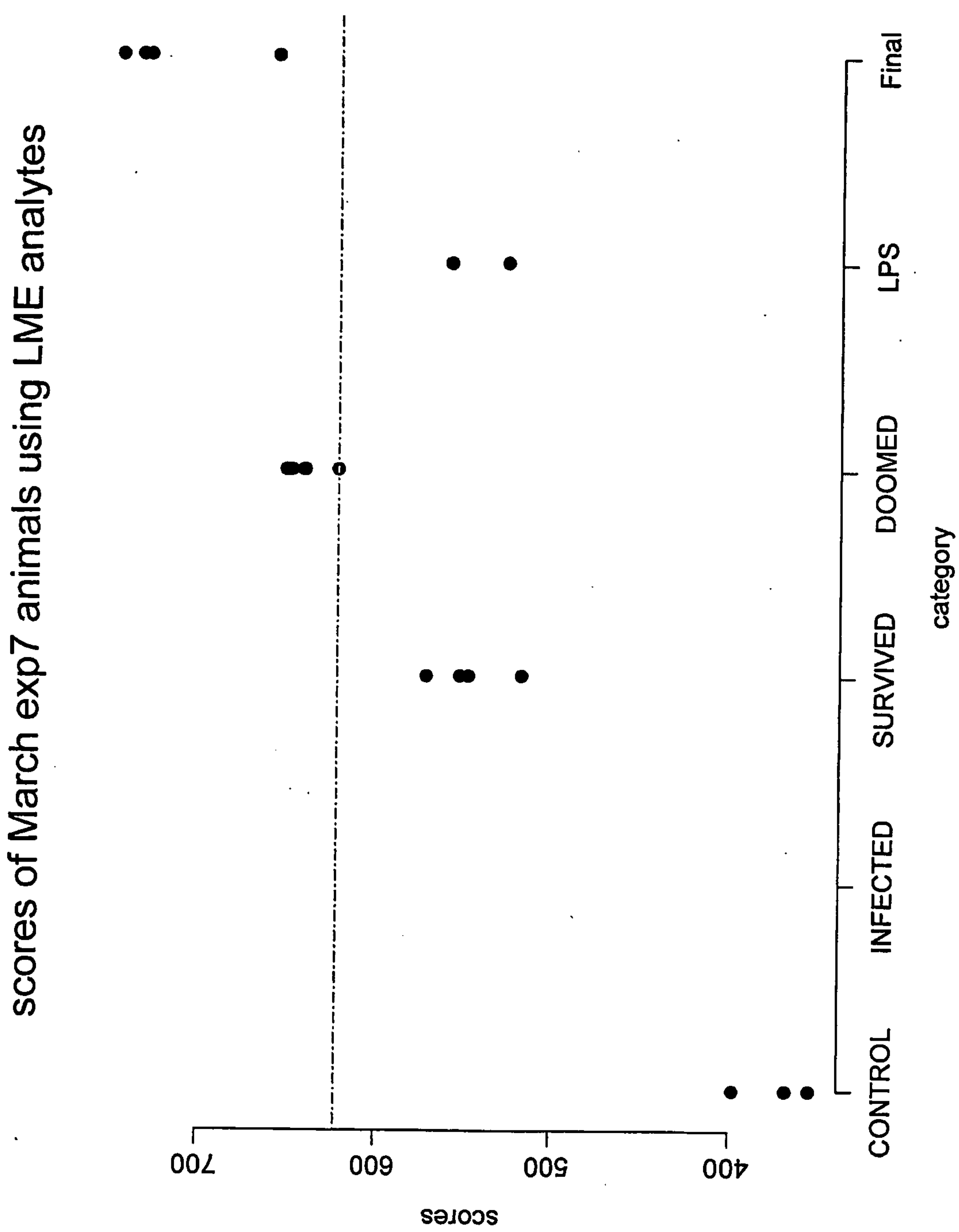
Cutoff 0.01: 11 analytes

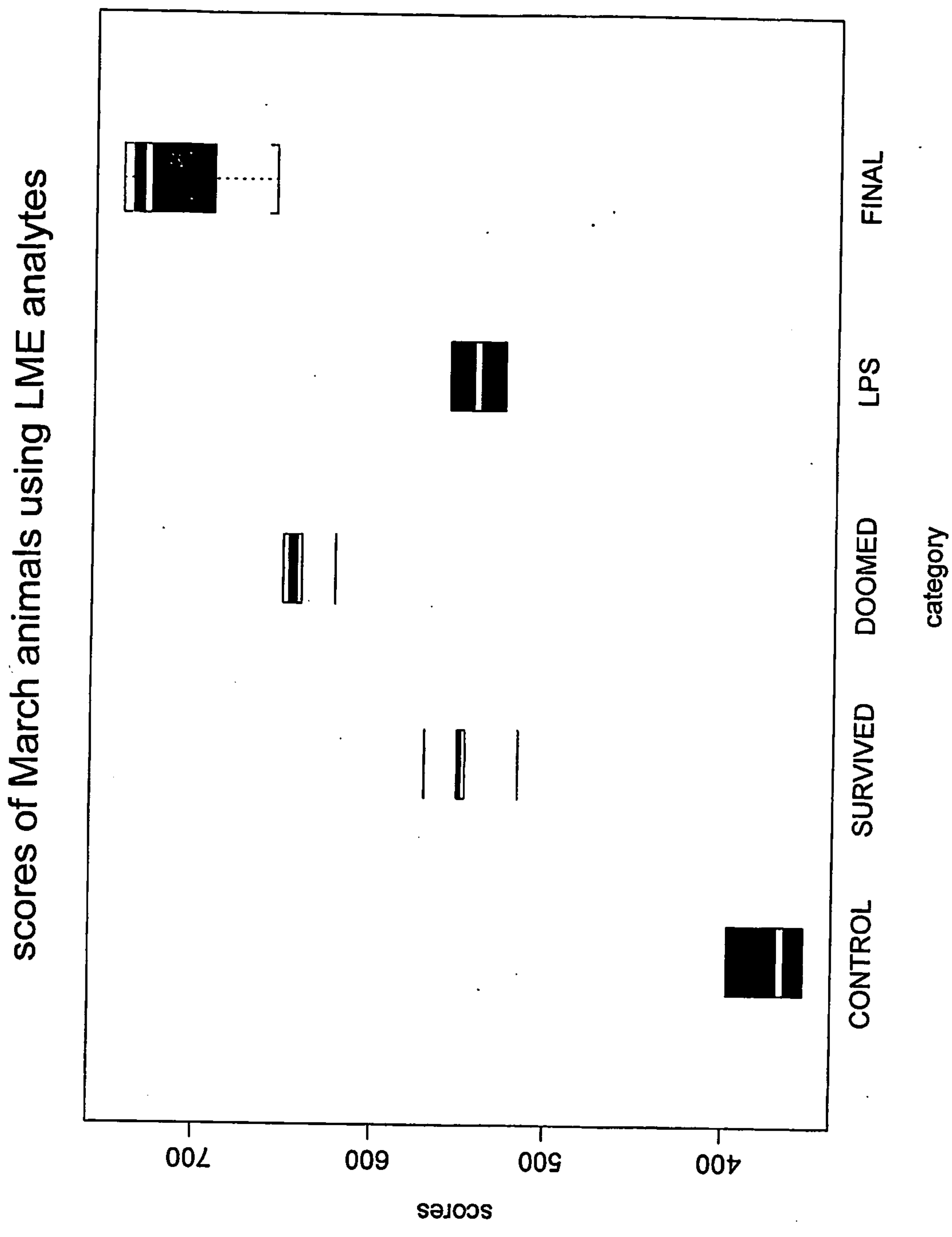
Cutoff 0.05: 14 analytes

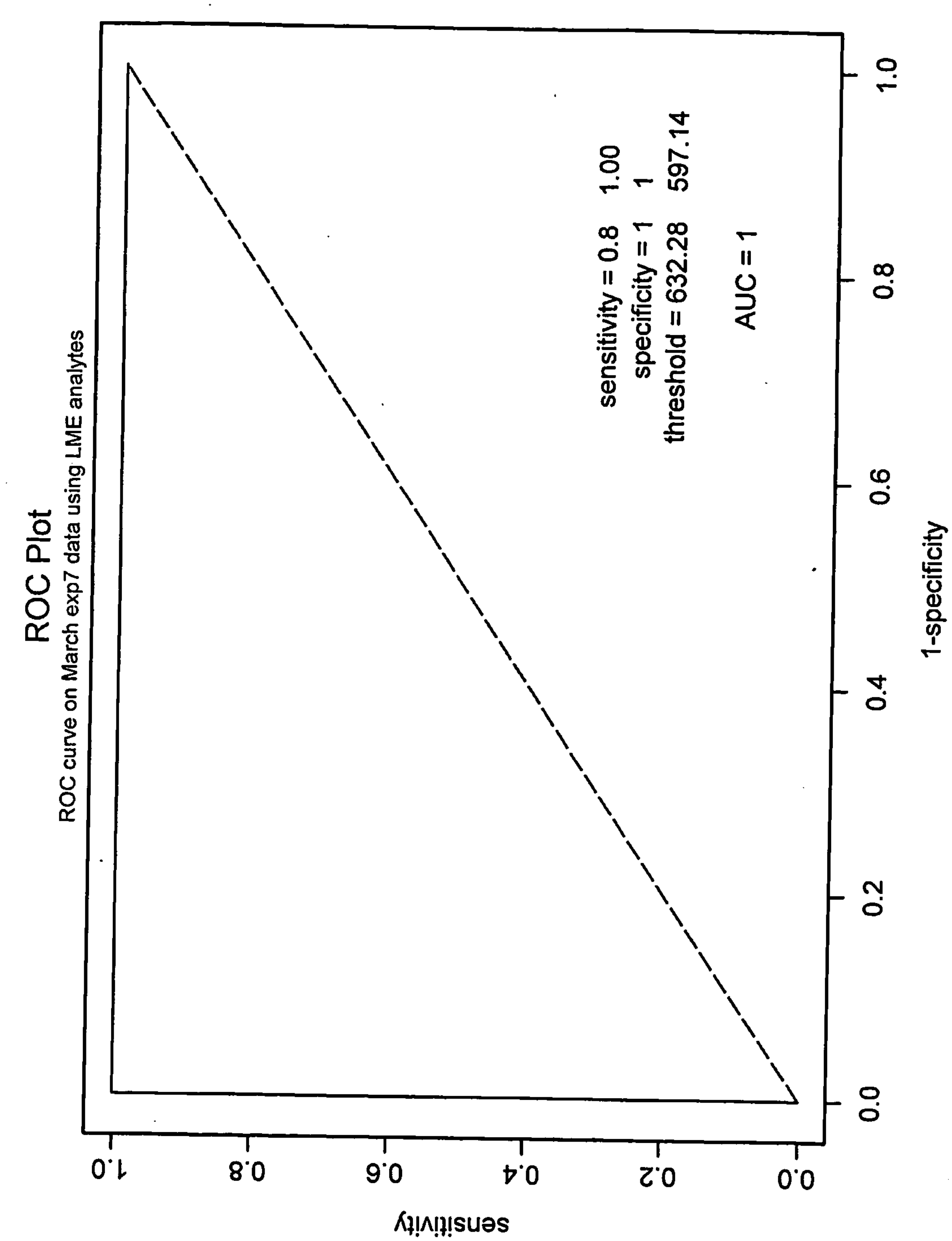
Weight of 11 analytes

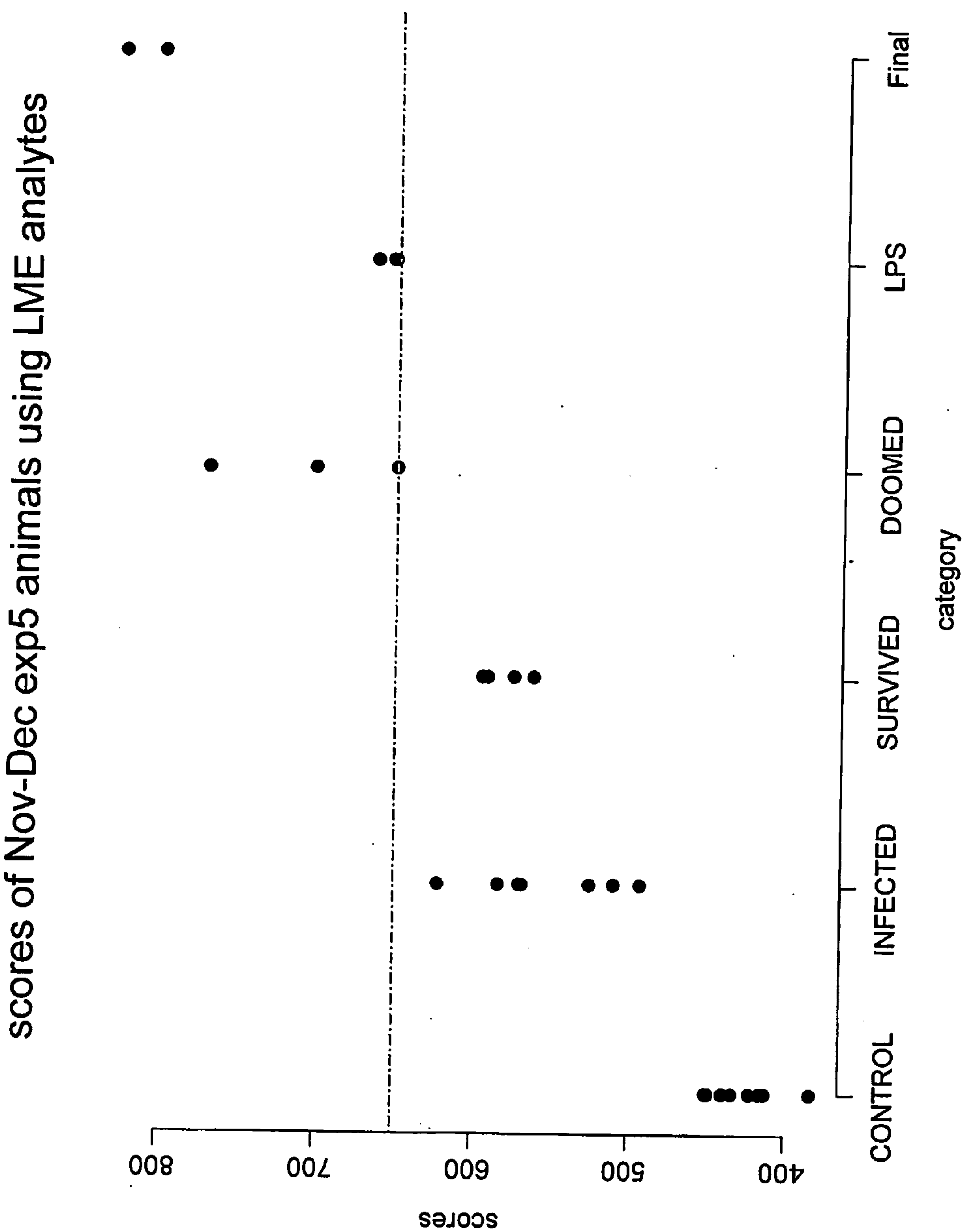
IL.6	MCP.1.JE	KC.GRO	MIP.1b	MIP.2	GCP.2
6.567	6.309	6.273	5.585	5.547	5.414

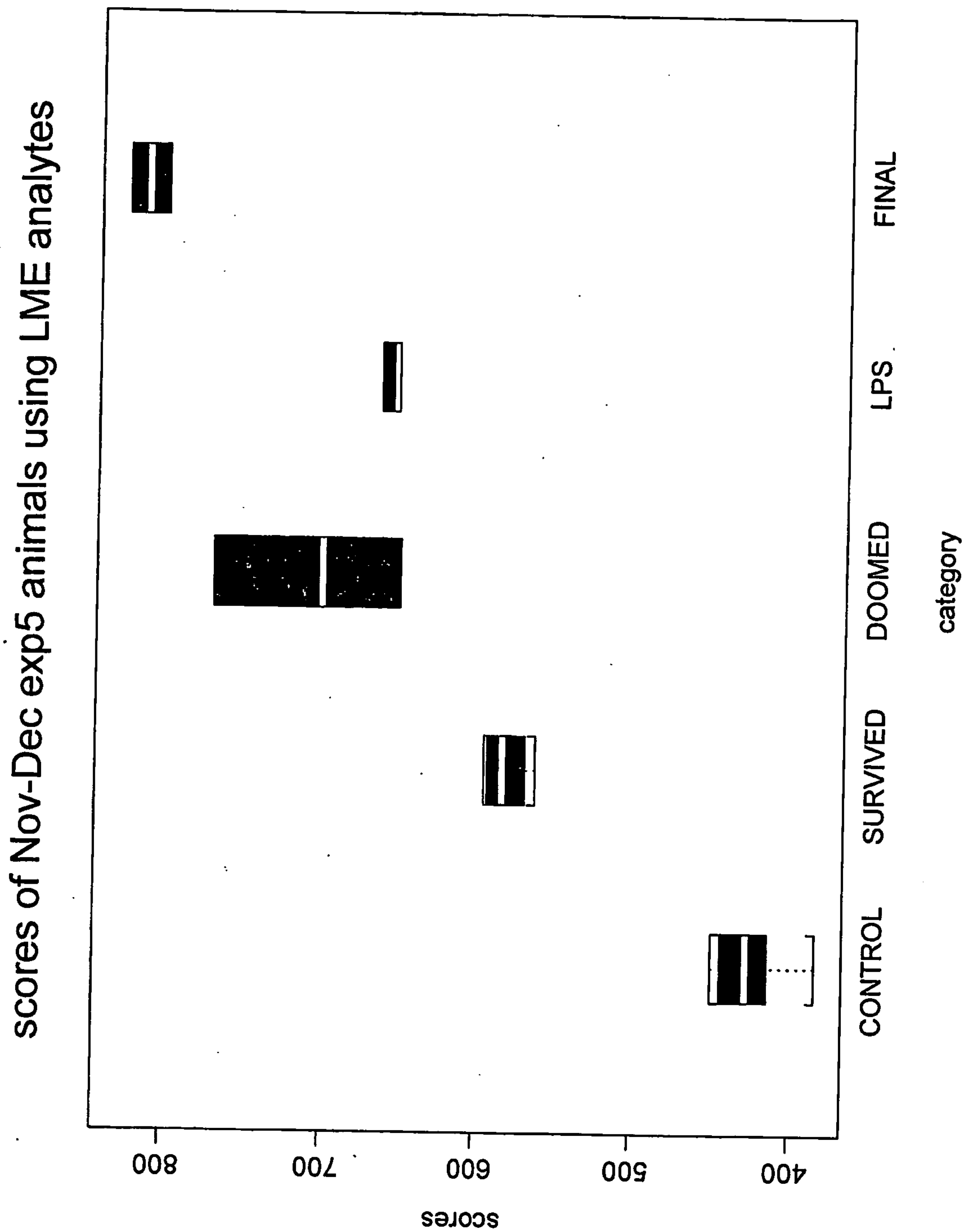
MCP.5	MCP.3	TIMP.1	TPO	IL.3
5.159	5.047	4.705	4.303	4.146

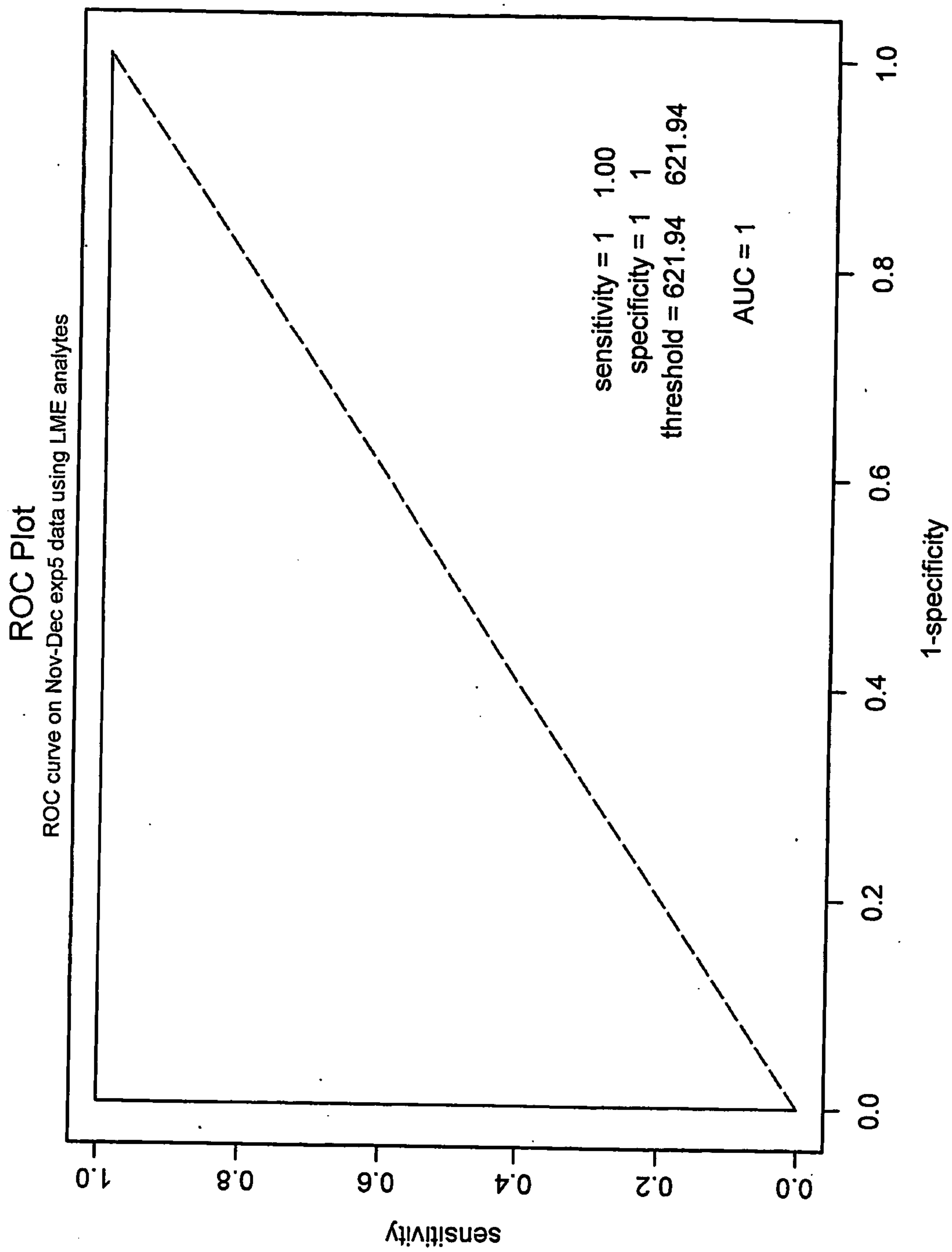

scores of March exp7 animals using LME analytes
scores
400
500
600
700
category
CONTROL
INFECTED
SURVIVED
DOOMED
LPS
Final

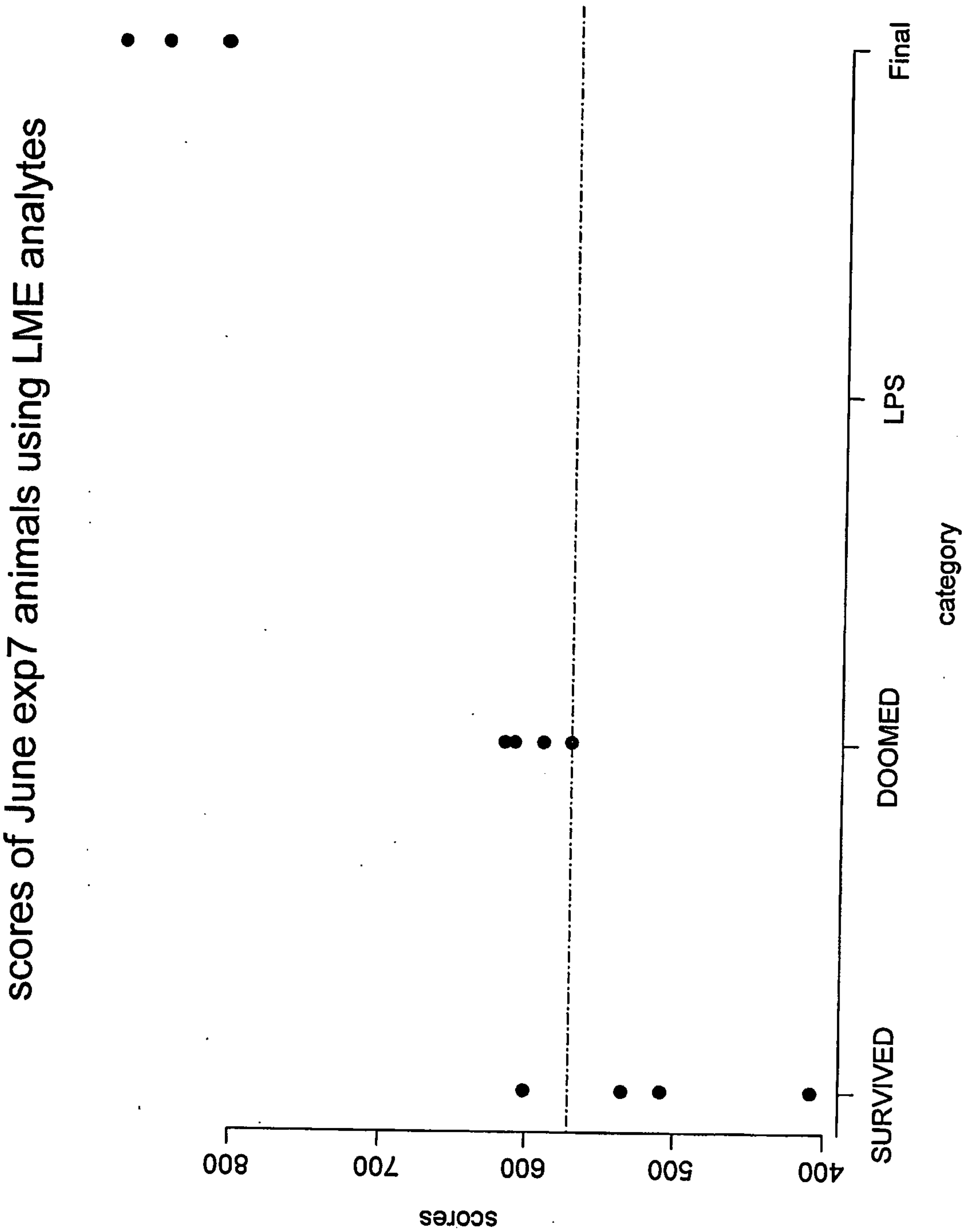

scores of March animals using LME analytes
scores
700
600
500
400
CONTROL
SURVIVED
DOOMED
LPS
FINAL
category

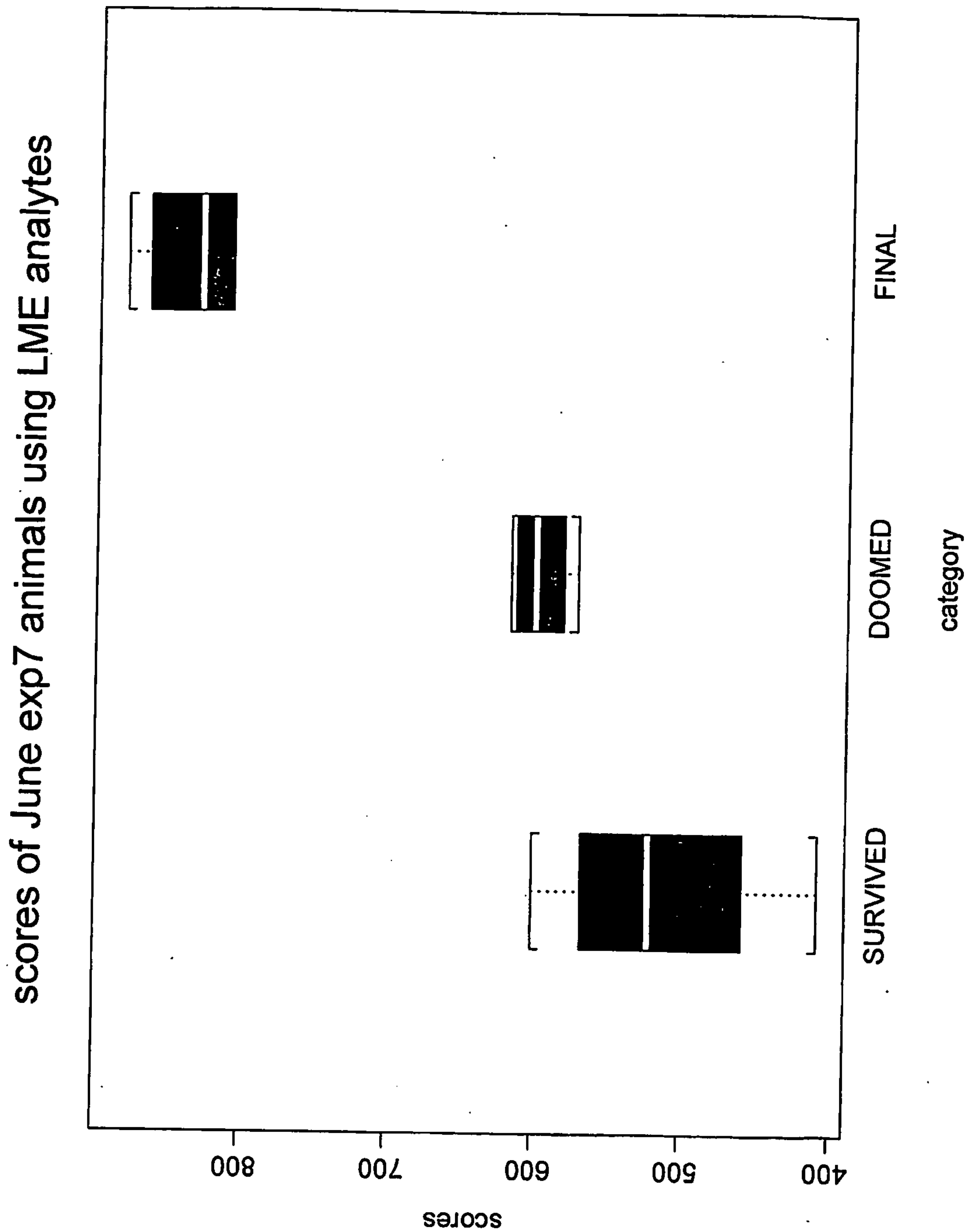

ROC Plot
ROC curve on March exp7 data using LME analytes
sensitivity = 0.8 1.00
specificity = 1 1
threshold = 632.28 597.14
AUC = 1
sensitivity
1-specificity
0.0
0.2
0.4
0.6
0.8
1.0

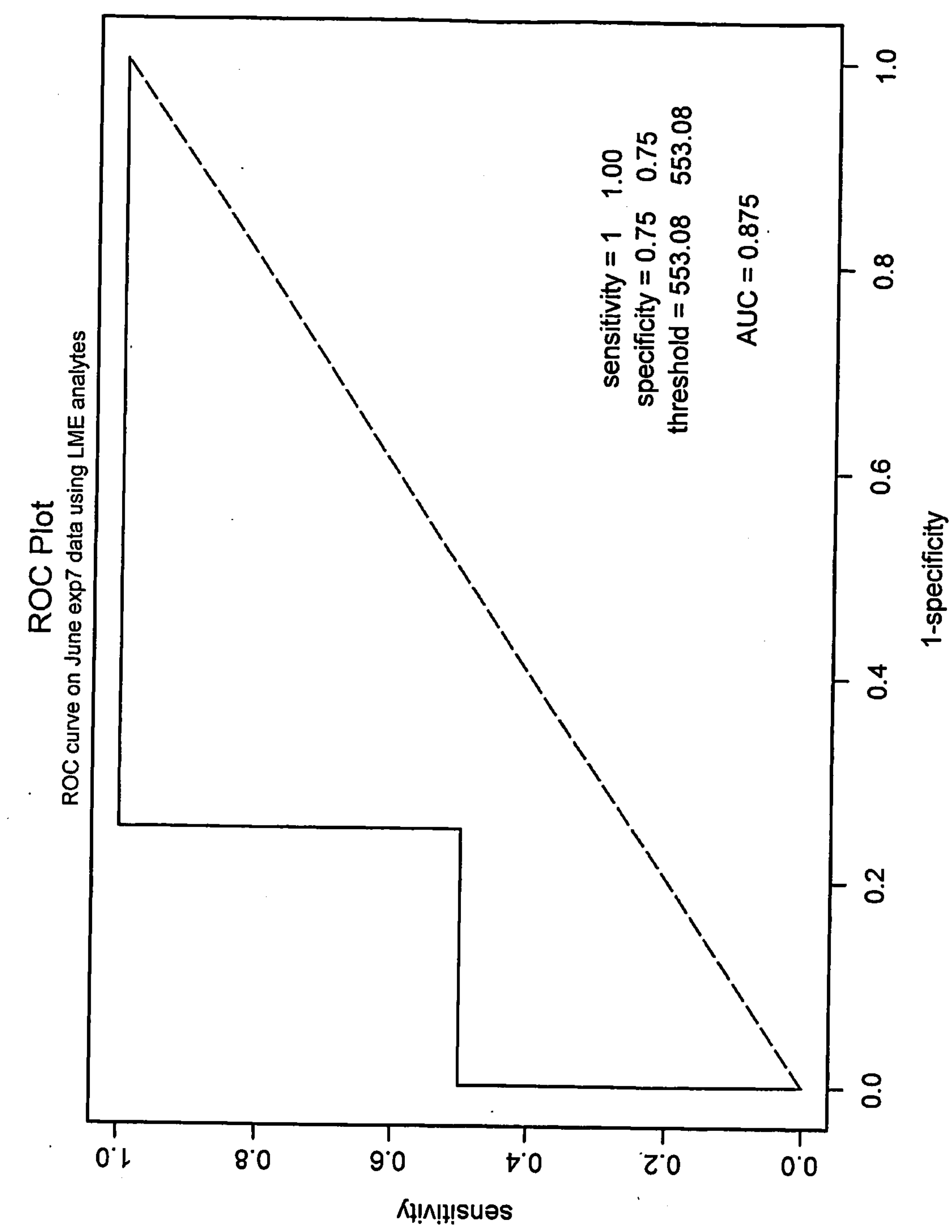

scores of Nov-Dec exp5 animals using LME analytes
scores
400
500
600
700
800
category
CONTROL
INFECTED
SURVIVED
DOOMED
LPS
Final

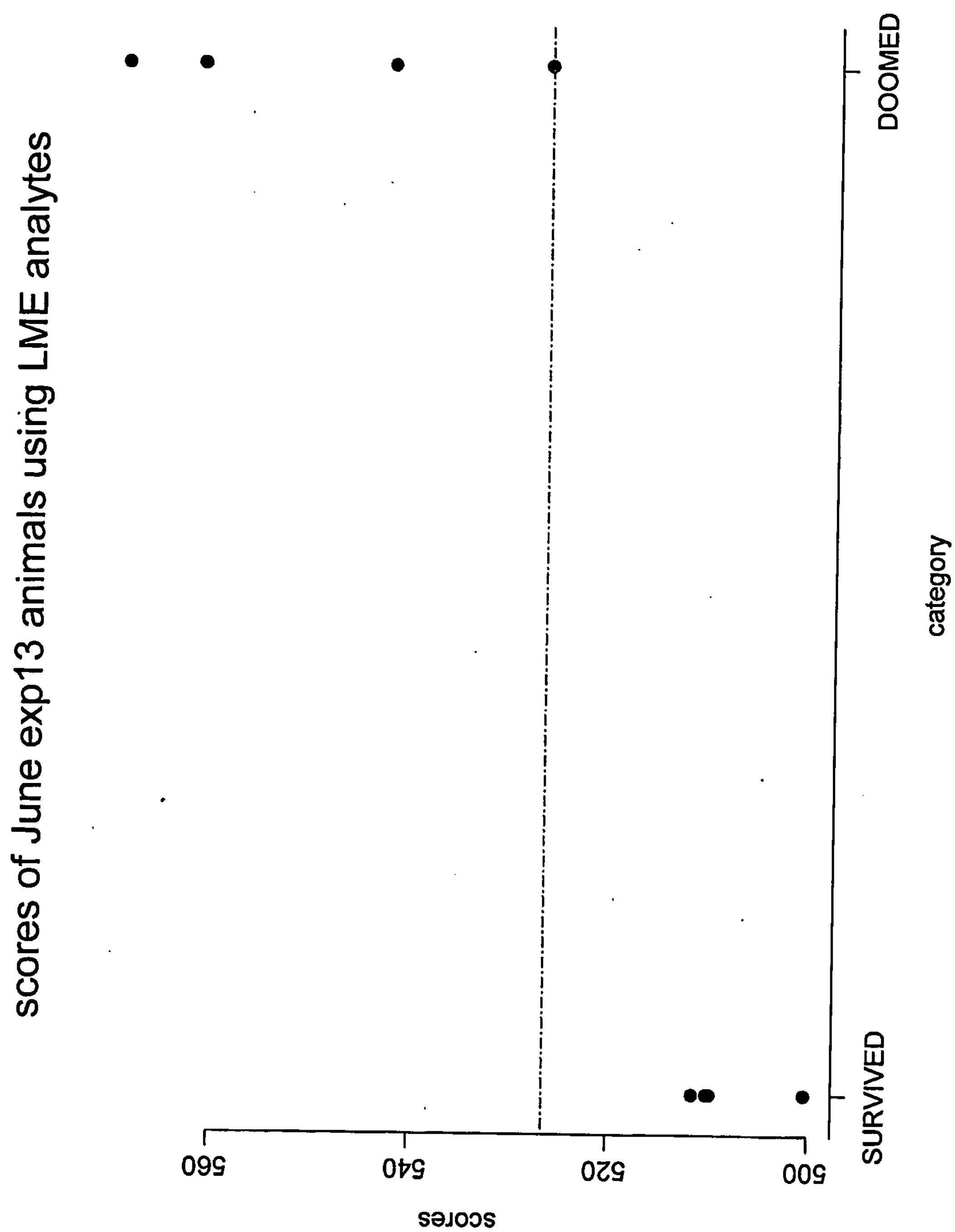

scores of Nov-Dec exp5 animals using LME analytes
scores
800
700
600
500
400
CONTROL
SURVIVED
DOOMED
LPS
FINAL
category

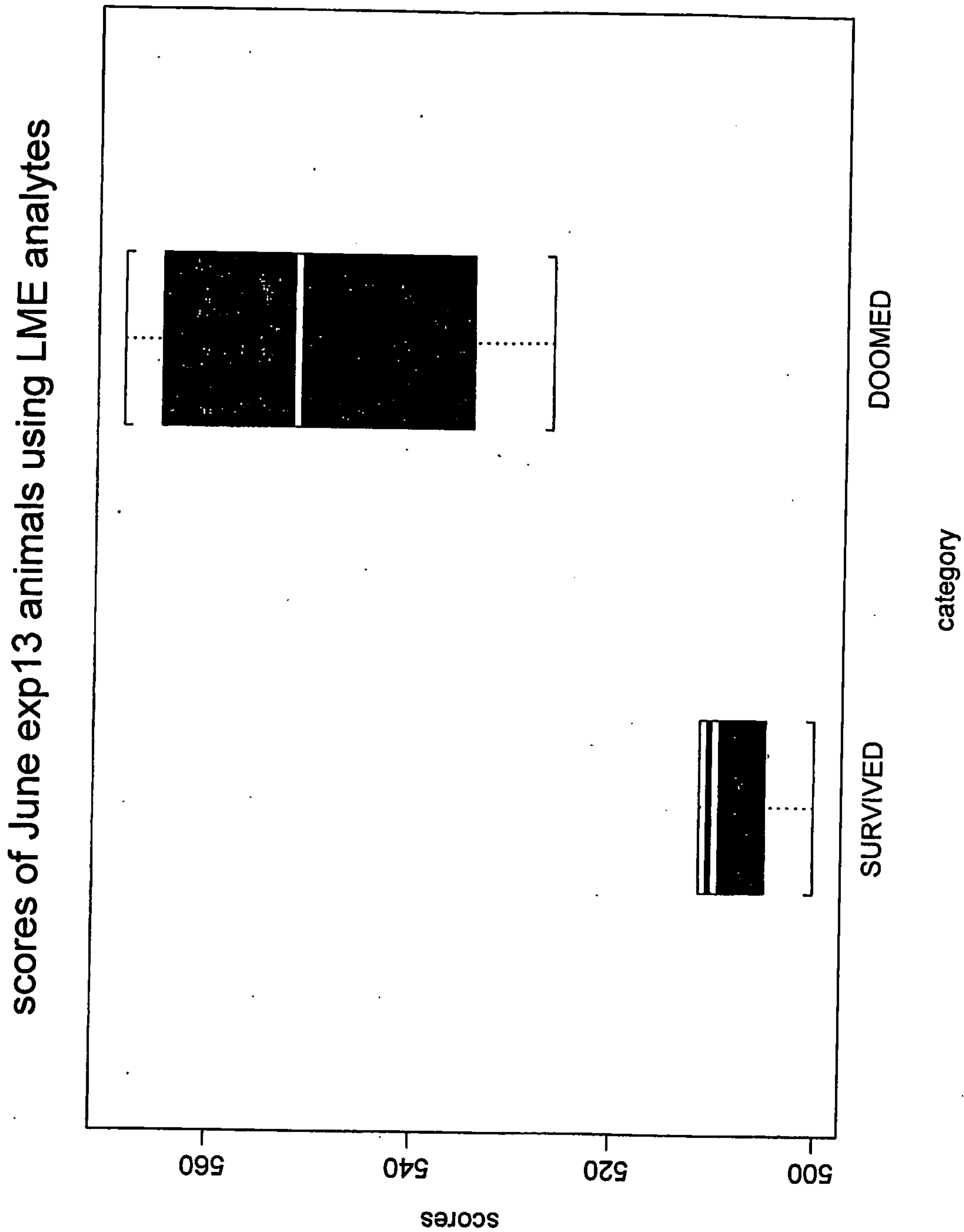

ROC Plot
ROC curve on Nov-Dec exp5 data using LME analytes
sensitivity = 1 1.00
specificity = 1 1
threshold = 621.94 621.94
AUC = 1
sensitivity
1-specificity
0.0
0.2
0.4
0.6
0.8
1.0

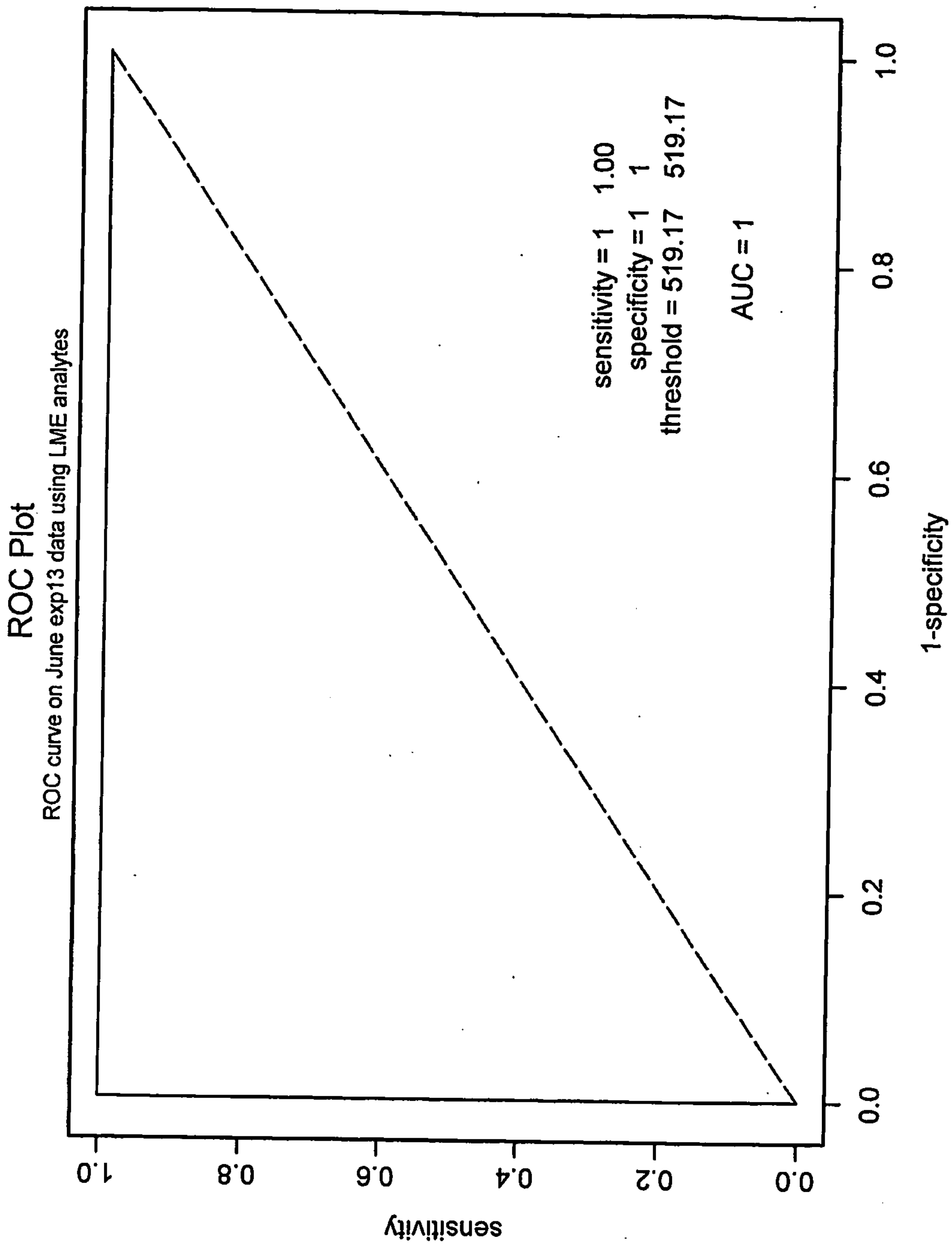

scores of June exp7 animals using LME analytes
scores
400
500
600
700
800
SURVIVED
DOOMED
LPS
Final
category

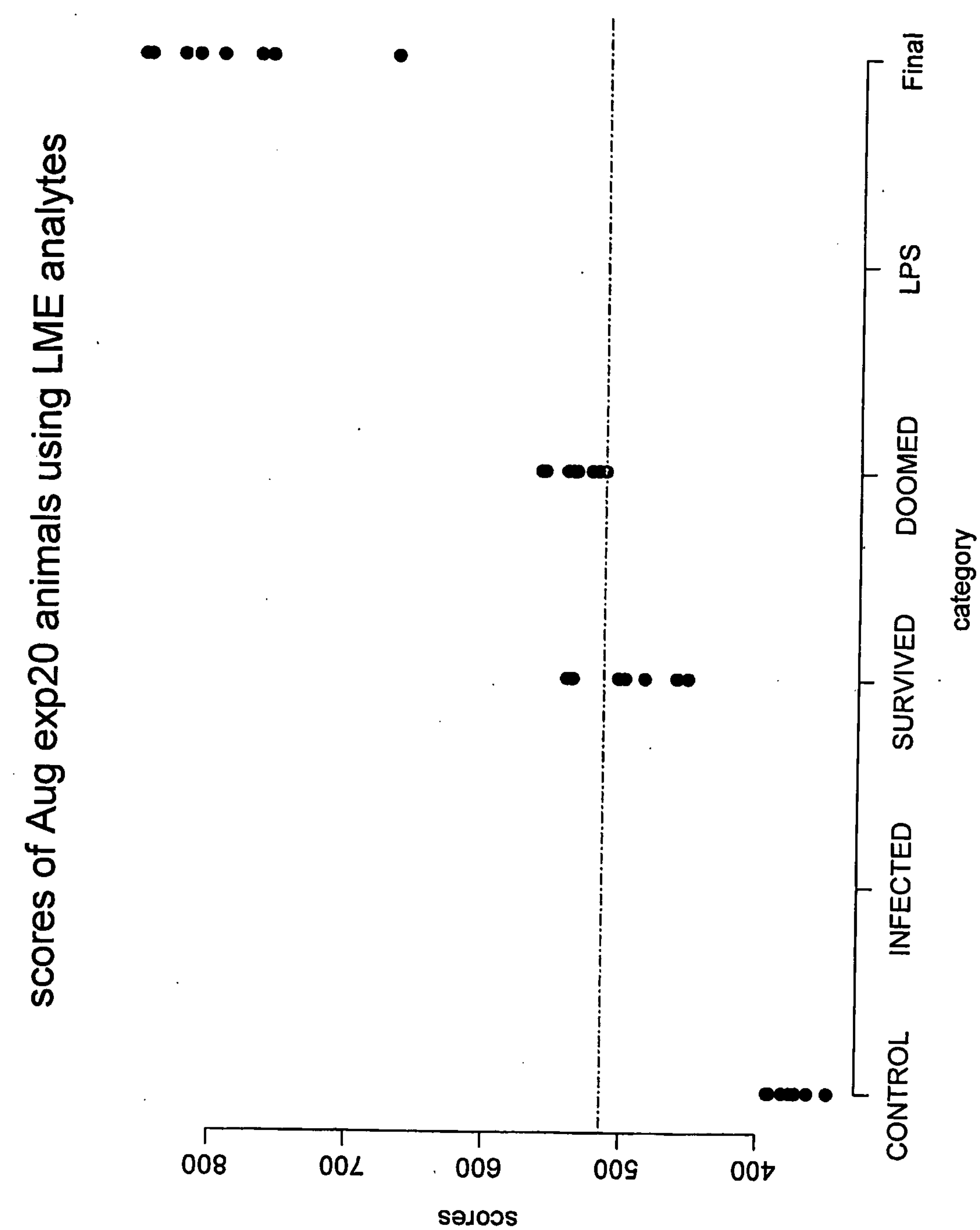

scores of June exp7 animals using LME analytes
scores
400
500
600
700
800
SURVIVED
DOOMED
FINAL
category

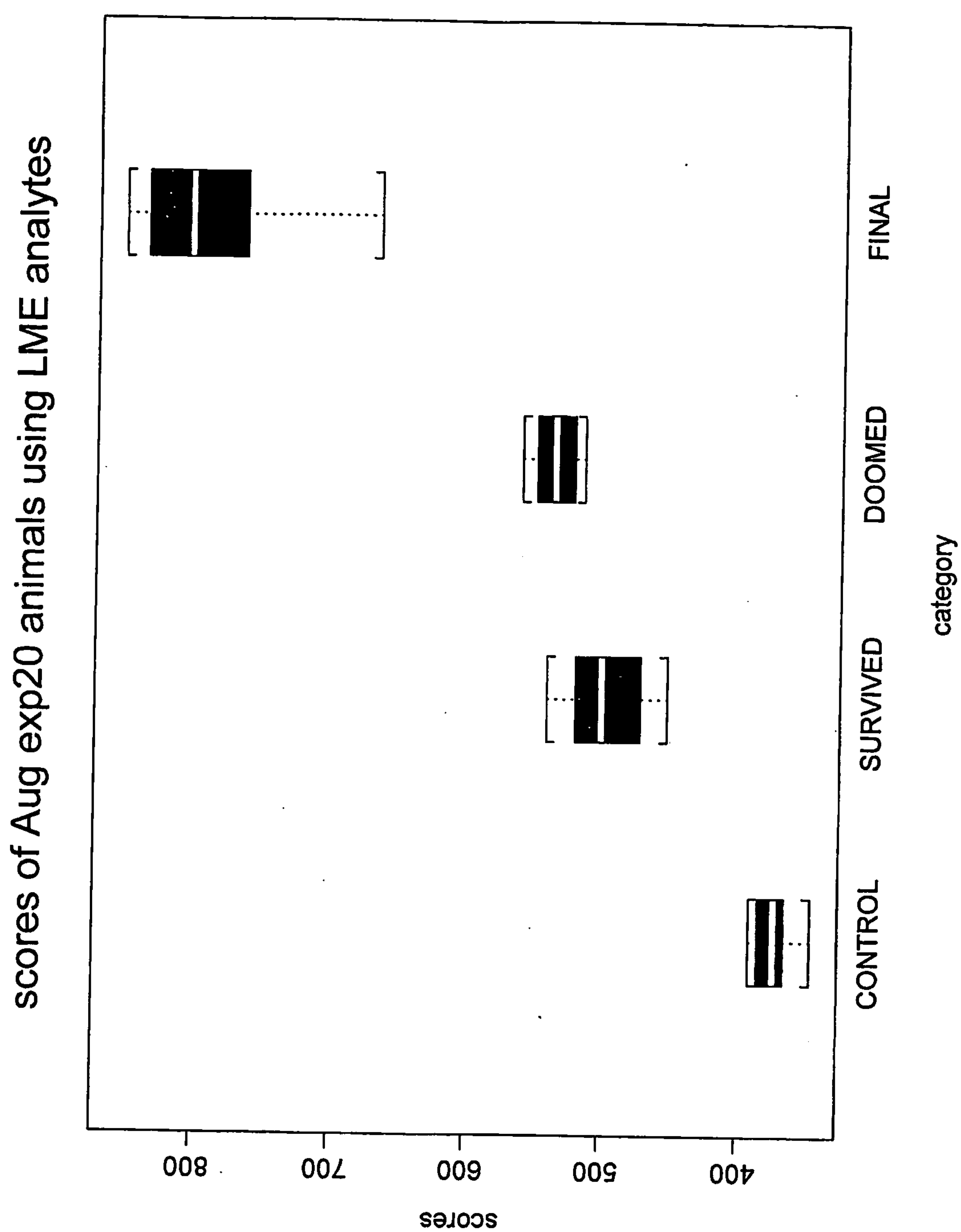

ROC Plot
ROC curve on June exp7 data using LME analytes
sensitivity = 1 1.00
specificity = 0.75 0.75
threshold = 553.08 553.08
AUC = 0.875
sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity
0.0
0.2
0.4
0.6
0.8
1.0

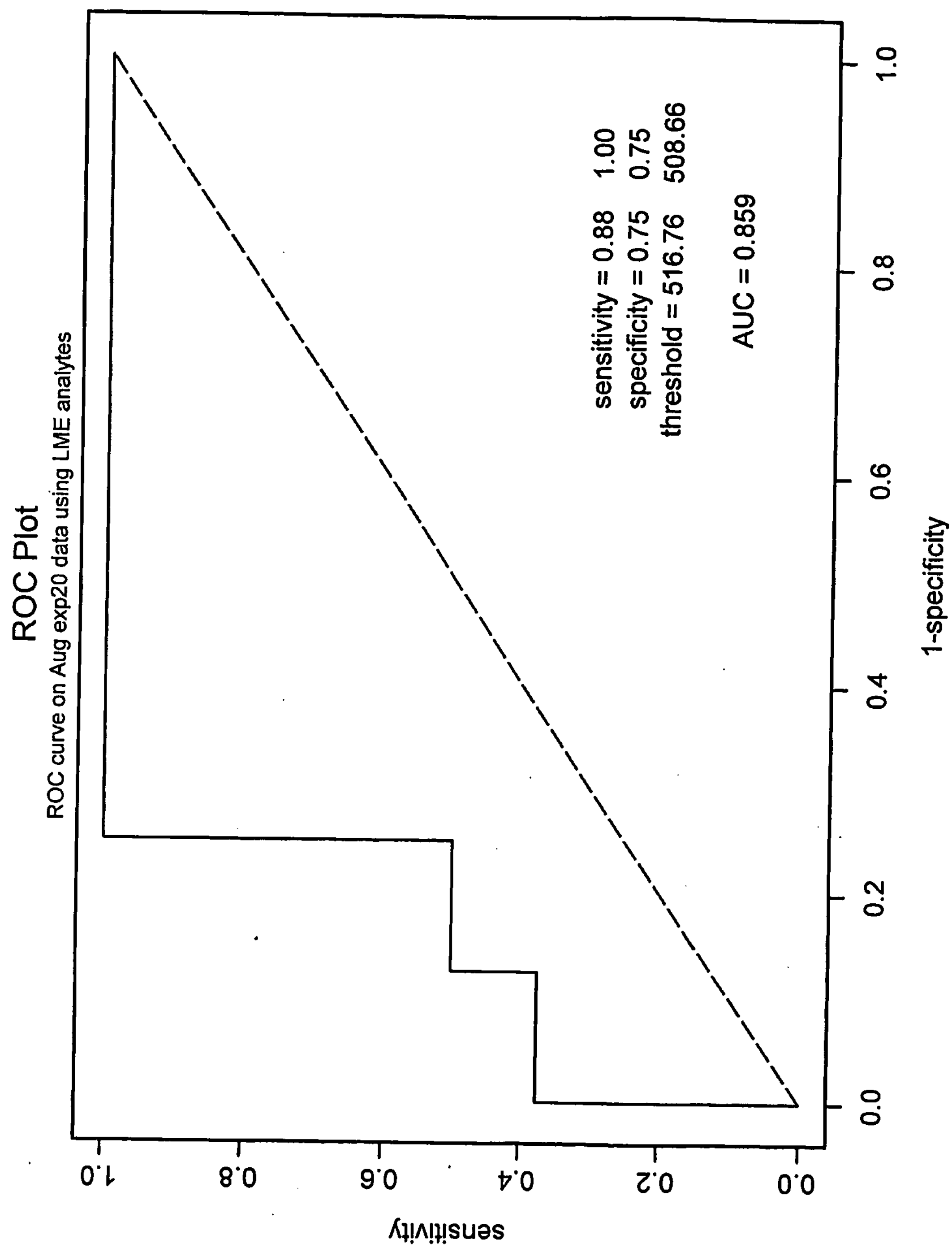

scores of June exp13 animals using LME analytes
scores
500
520
540
560
category
SURVIVED
DOOMED

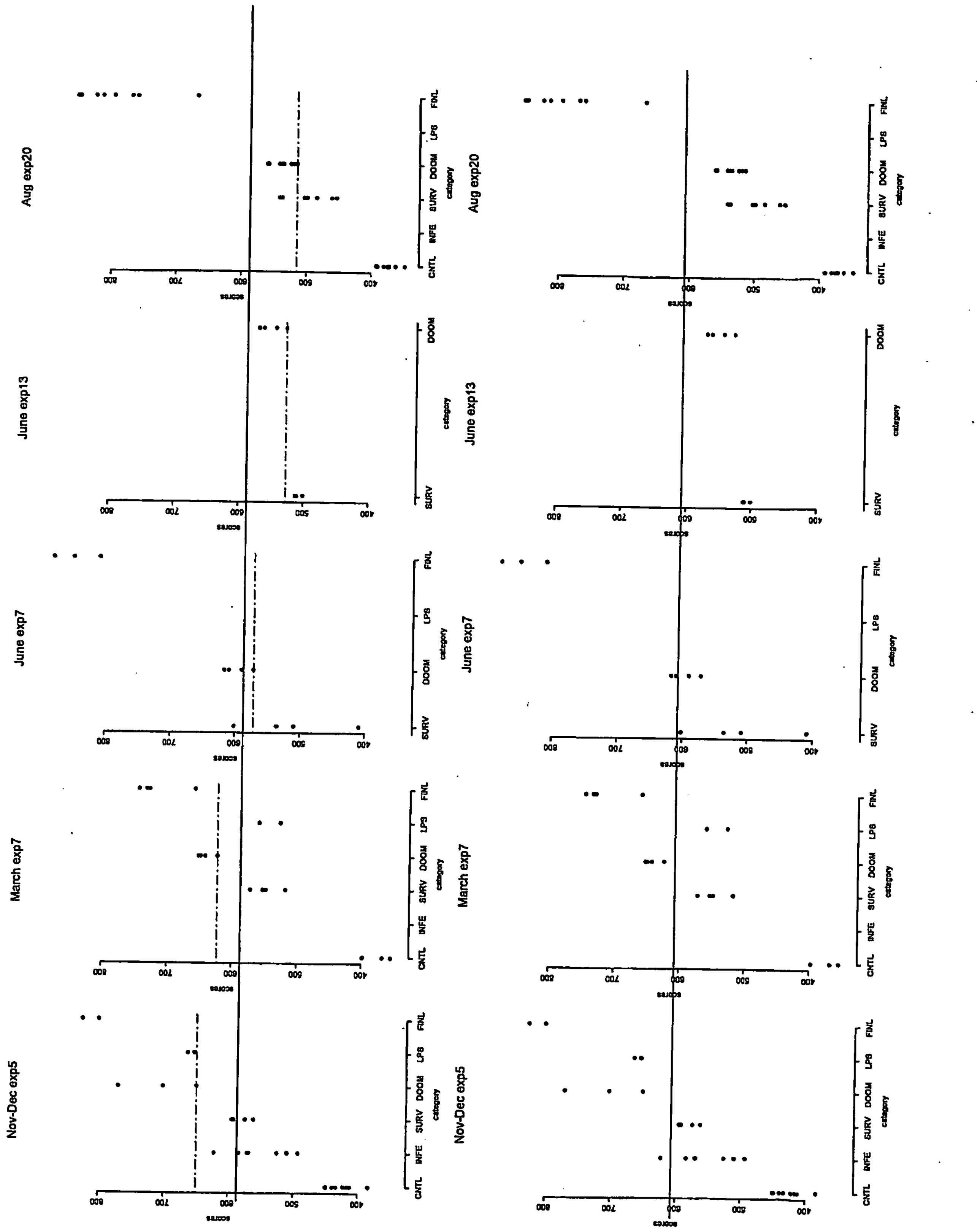

scores of June exp13 animals using LME analytes
DOOMED
SURVIVED
category
scores
560
540
520
500


ROC Plot
ROC curve on June exp13 data using LME analytes
sensitivity = 1 1.00
specificity = 1 1
threshold = 519.17 519.17
AUC = 1
1-specificity
sensitivity
0.0
0.2
0.4
0.6
0.8
1.0


scores of Aug exp20 animals using LME analytes
scores
400
500
600
700
800
CONTROL
INFECTED
SURVIVED
DOOMED
LPS
Final
category


scores of Aug exp20 animals using LME analytes
scores
800
700
600
500
400
category
CONTROL
SURVIVED
DOOMED
FINAL


ROC Plot
ROC curve on Aug exp20 data using LME analytes
sensitivity = 0.88 1.00
specificity = 0.75 0.75
threshold = 516.76 508.66
AUC = 0.859
sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity
0.0
0.2
0.4
0.6
0.8
1.0

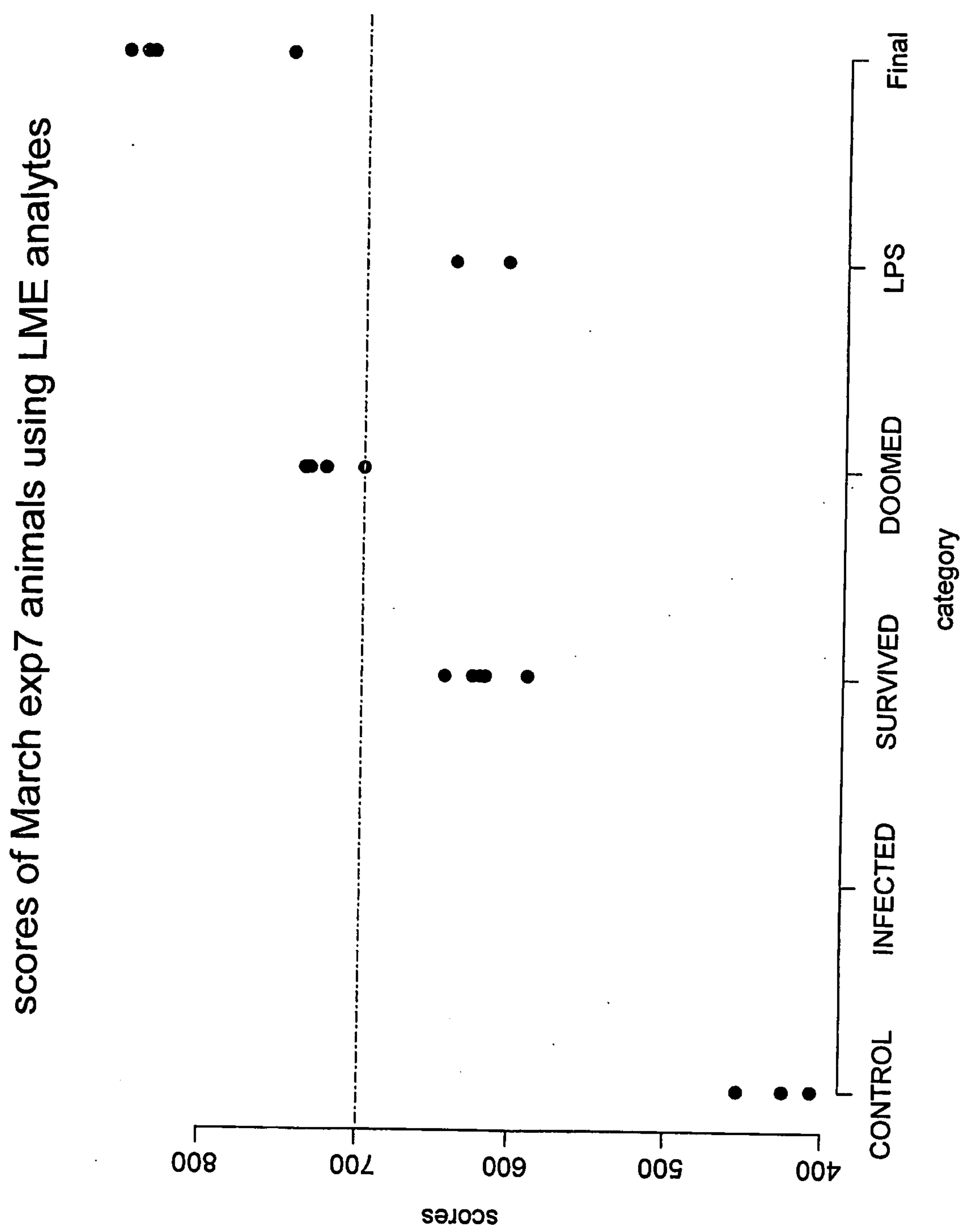

Aug exp20
June exp13
June exp7
March exp7
Nov-Dec exp5
scores
category
CNTL
INFE
SURV
DOOM
LPS
FINL

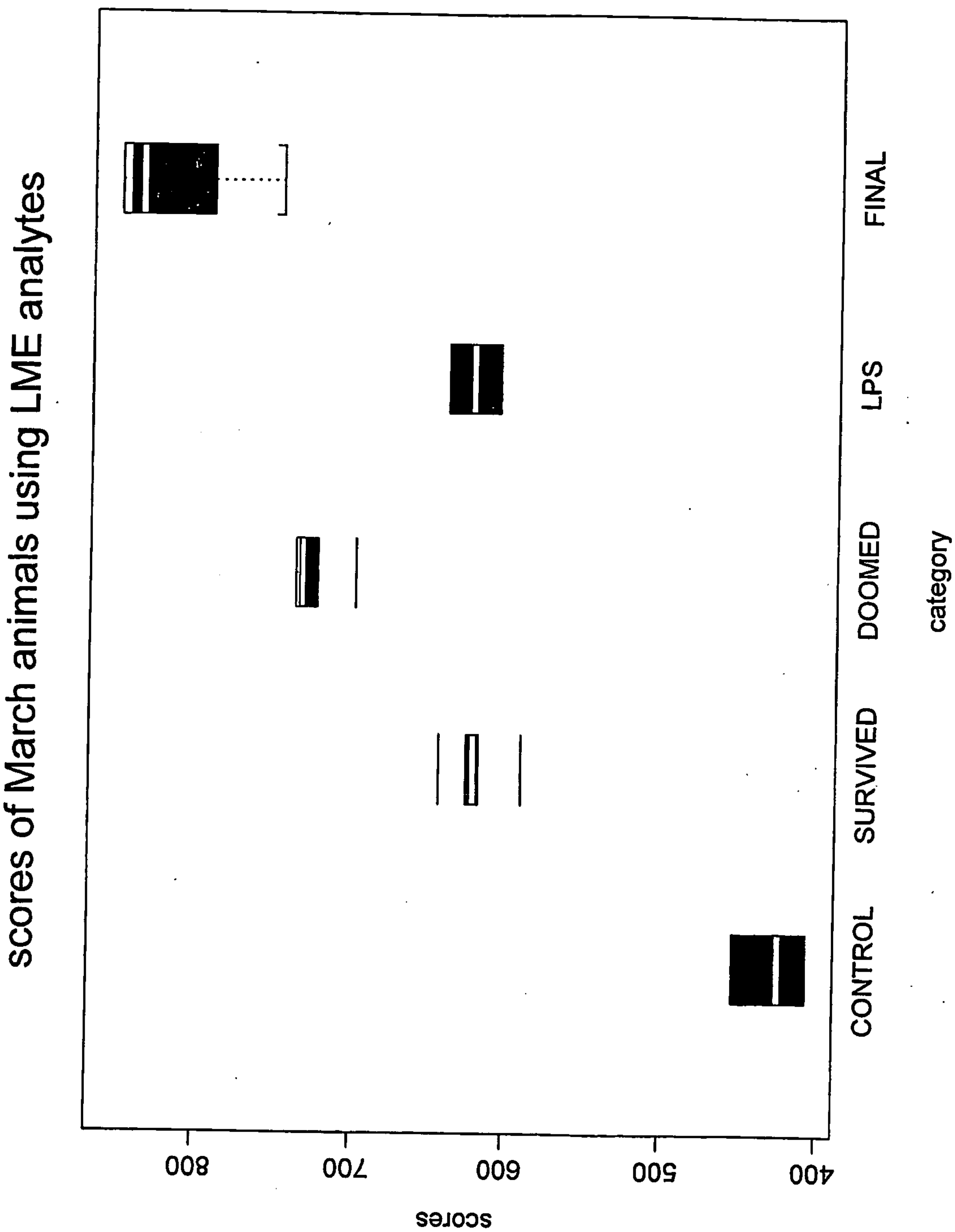
Weight of 14 analytes

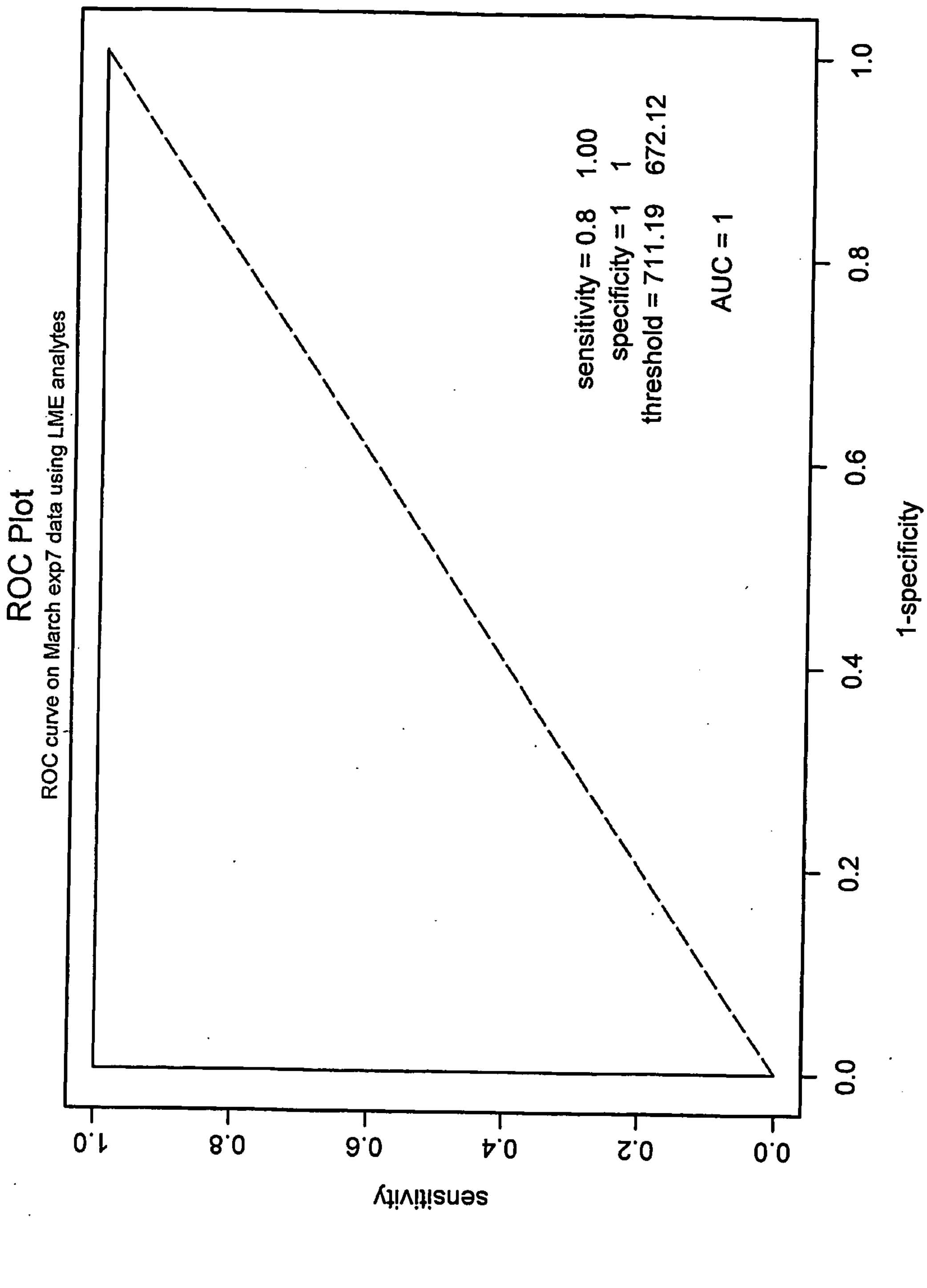
IL.6 MCP.1.JE KC.GRO MIP.1b MIP.2 GCP.2 MCP.5

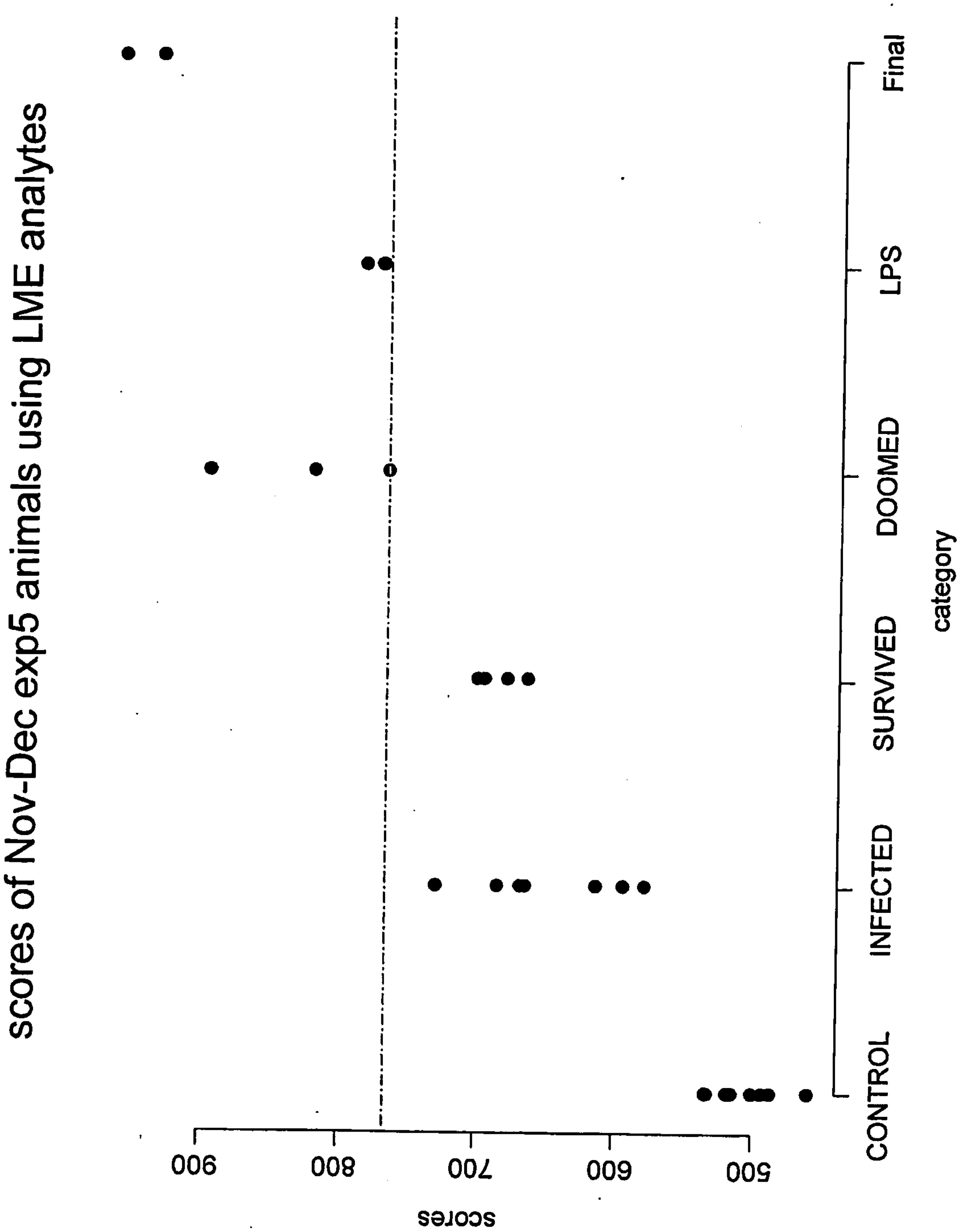
6.567 6.309 6.273 5.585 5.547 5.414 5.159

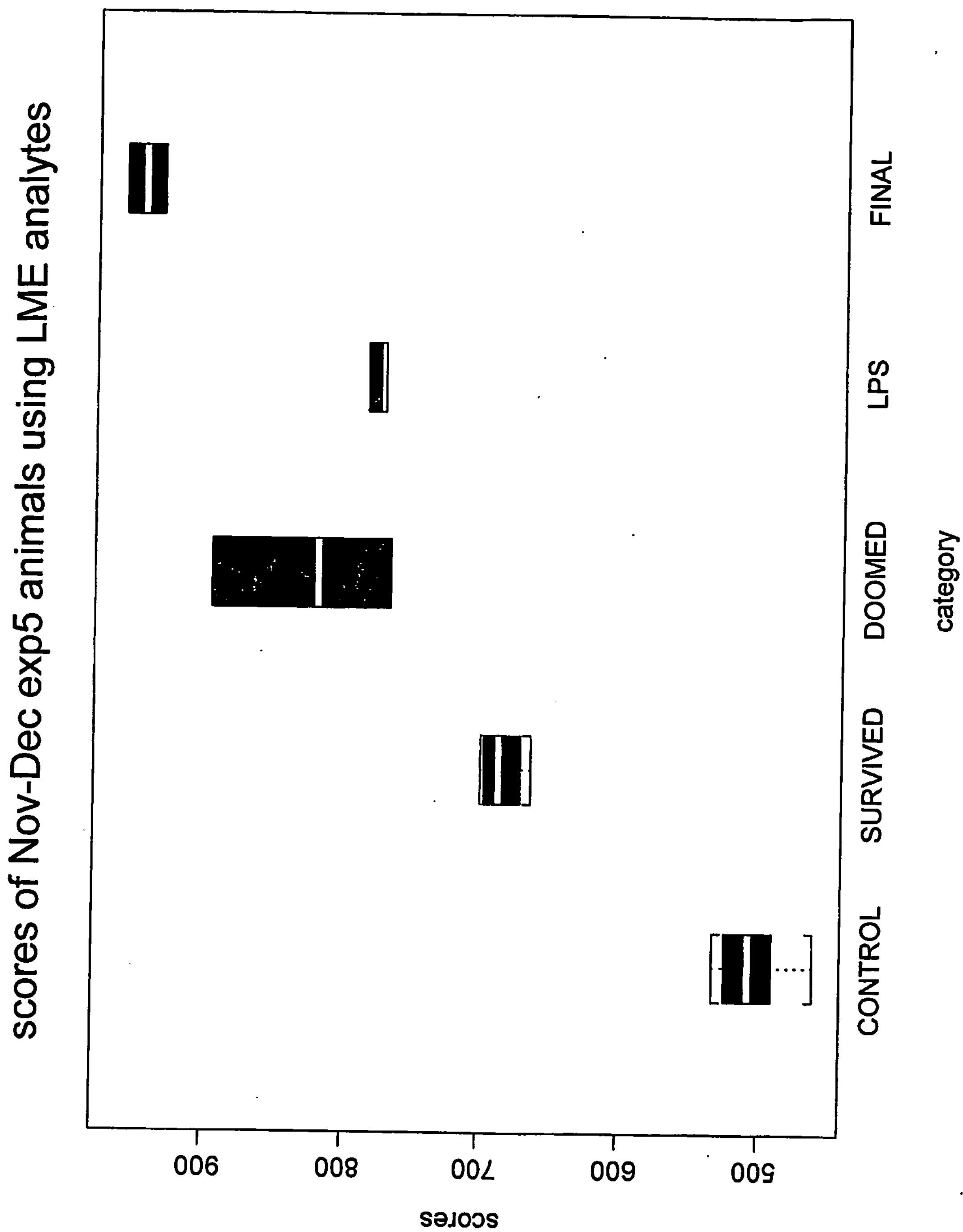
MCP.3 TIMP.1 TPO IL.3 IL.10 VEGF TNFa 5.047 4.705
4.303 4.146 4 3.821 3.779

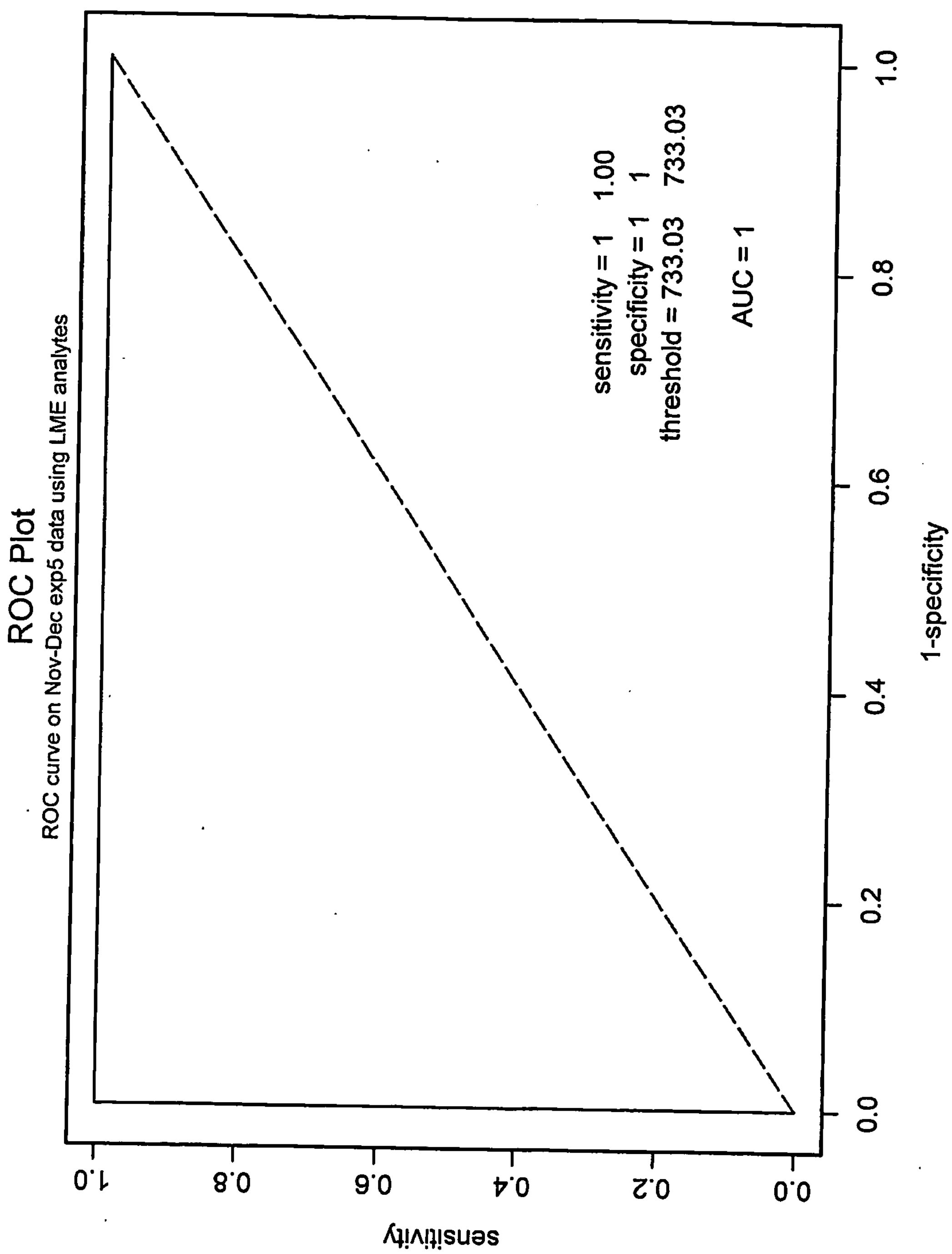

scores of March exp7 animals using LME analytes
scores
400
500
600
700
800
category
CONTROL
INFECTED
SURVIVED
DOOMED
LPS
Final

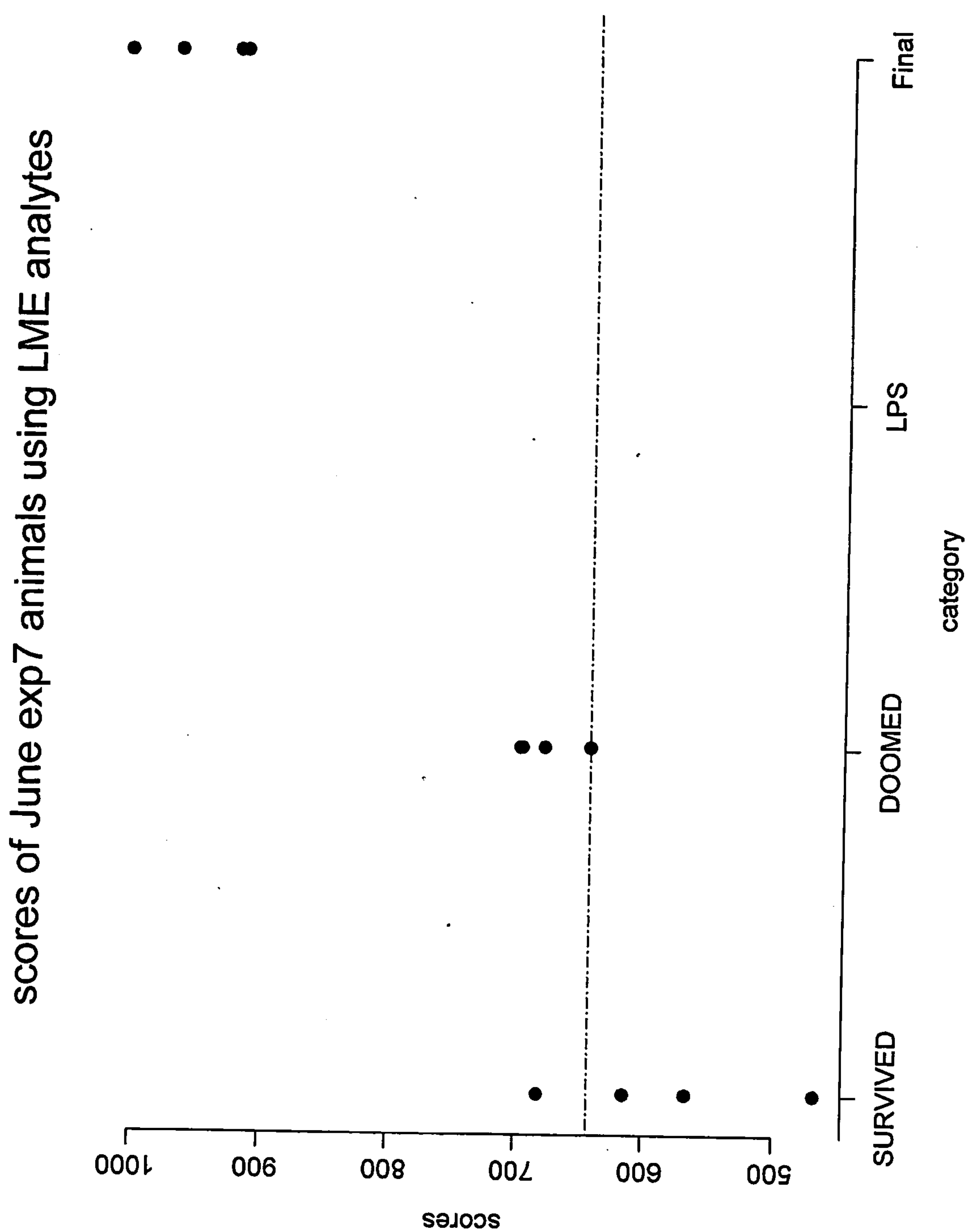

scores of March animals using LME analytes
scores
400
500
600
700
800
CONTROL
SURVIVED
DOOMED
LPS
FINAL
category

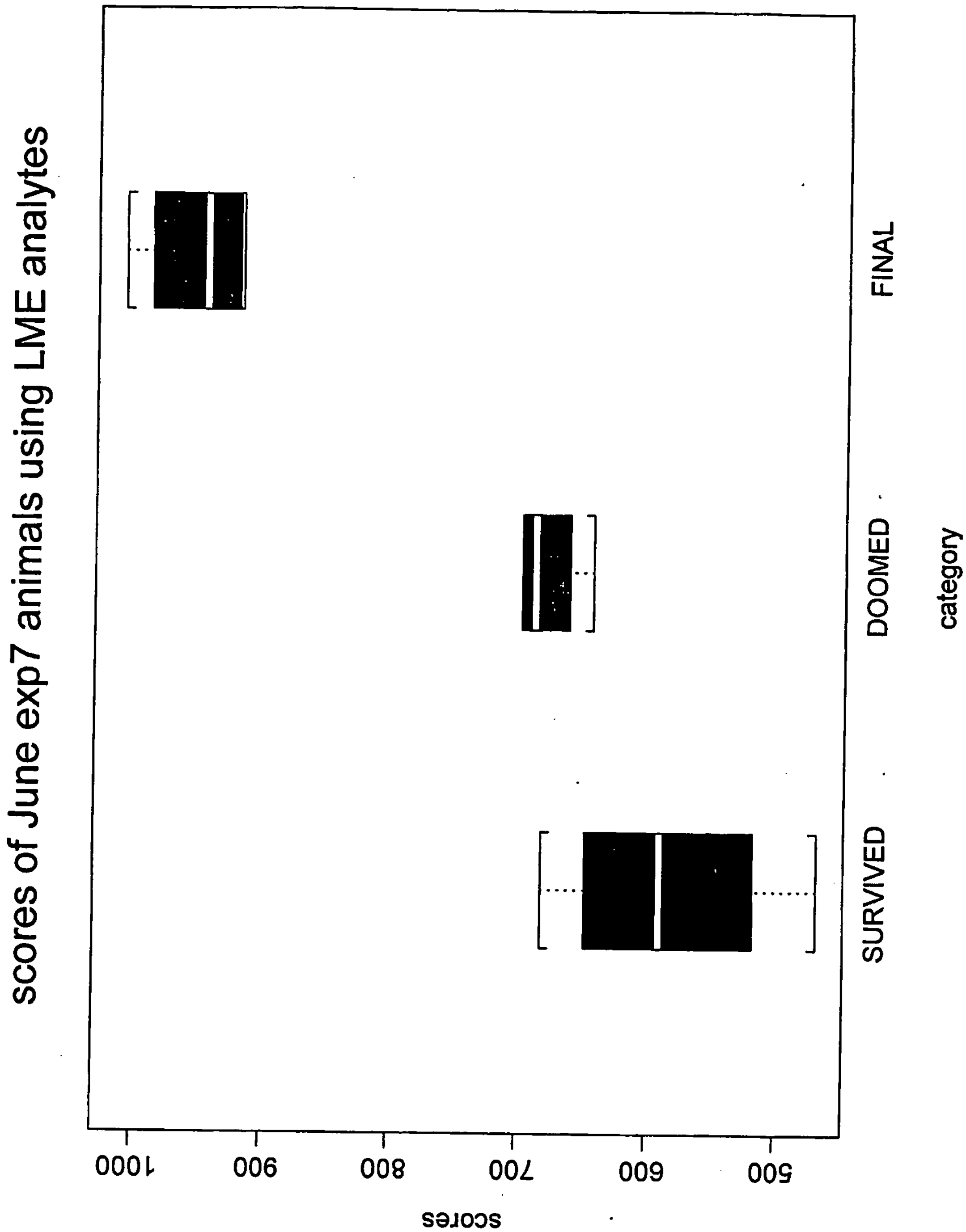

ROC Plot
ROC curve on March exp7 data using LME analytes
sensitivity = 0.8 1.00
specificity = 1 1
threshold = 711.19 672.12
AUC = 1
1-specificity
sensitivity
0.0
0.2
0.4
0.6
0.8
1.0

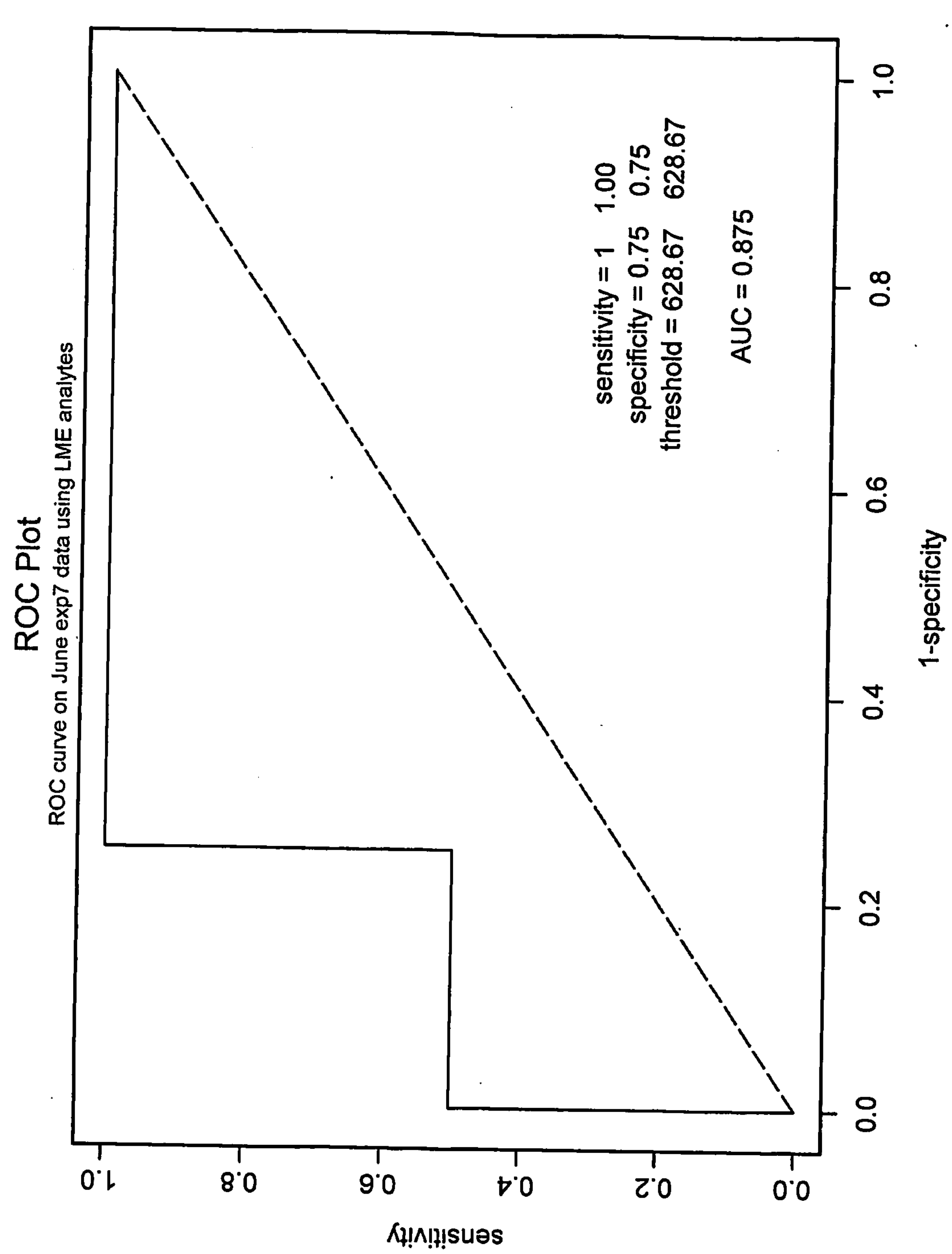

scores of Nov-Dec exp5 animals using LME analytes
scores
500
600
700
800
900
category
CONTROL
INFECTED
SURVIVED
DOOMED
LPS
Final

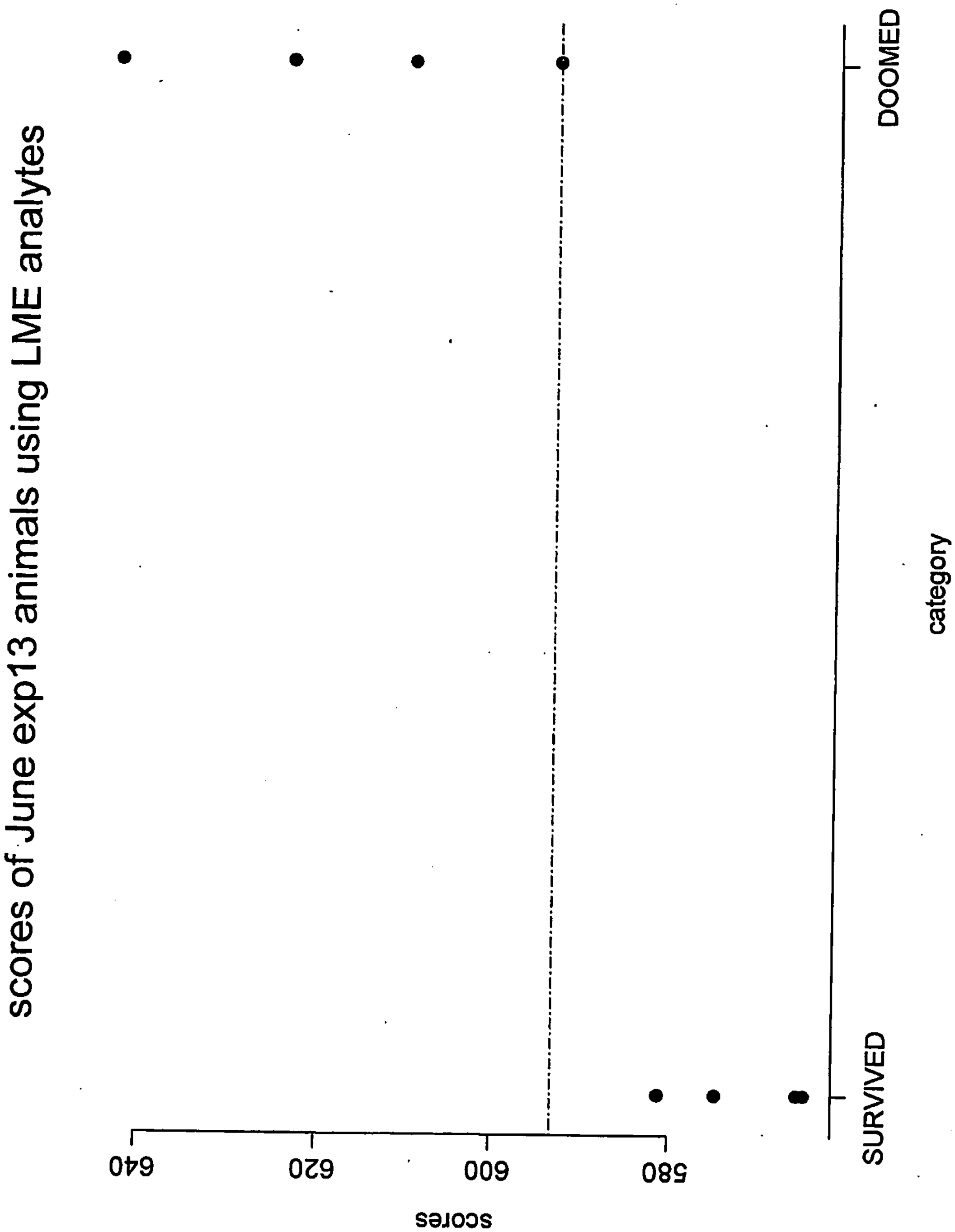

scores of Nov-Dec exp5 animals using LME analytes
CONTROL
SURVIVED
DOOMED
LPS
FINAL
category
500
600
700
800
900
scores

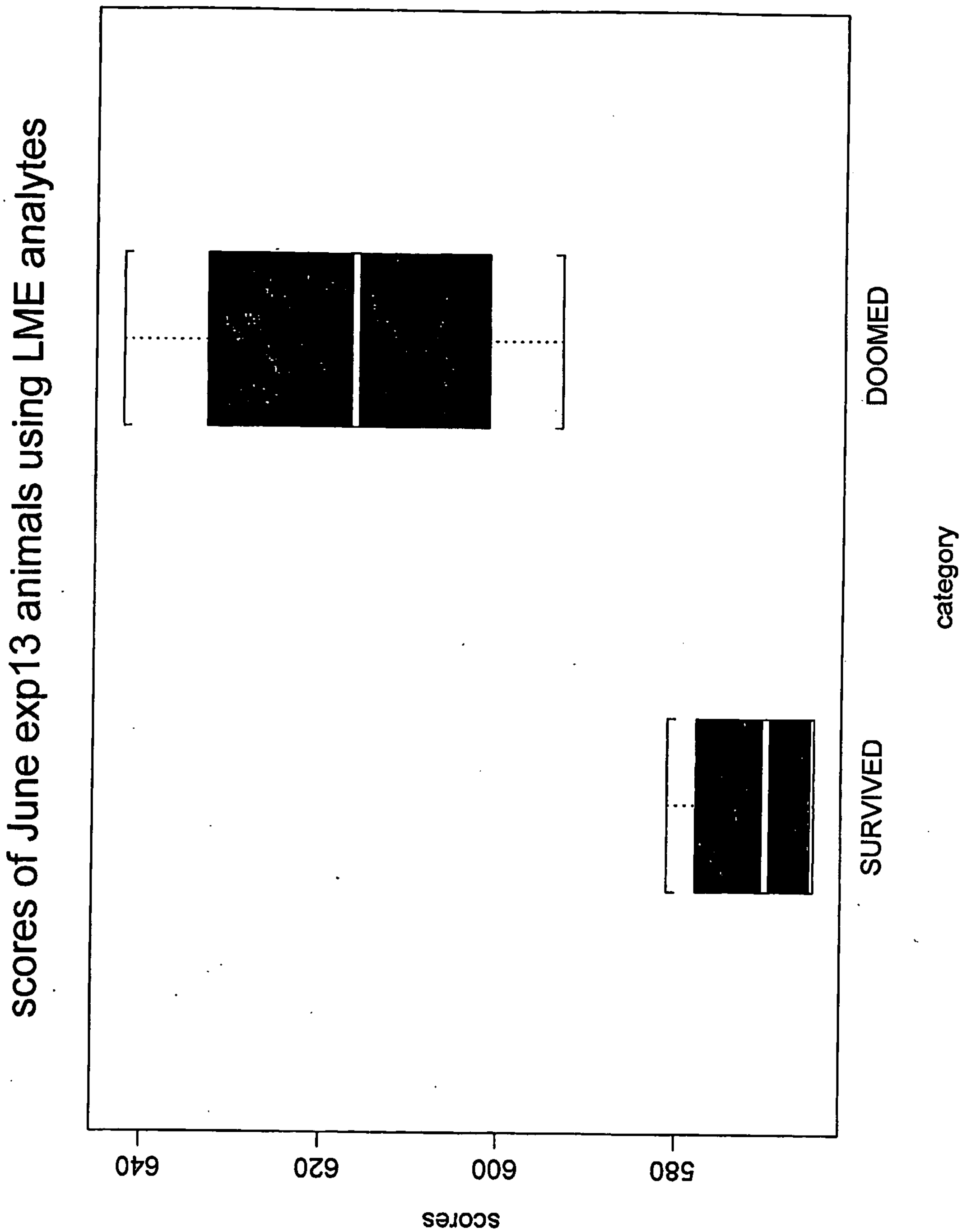

ROC Plot
ROC curve on Nov-Dec exp5 data using LME analytes
sensitivity = 1 1.00
specificity = 1 1
threshold = 733.03 733.03
AUC = 1
sensitivity
1-specificity
0.0
0.2
0.4
0.6
0.8
1.0

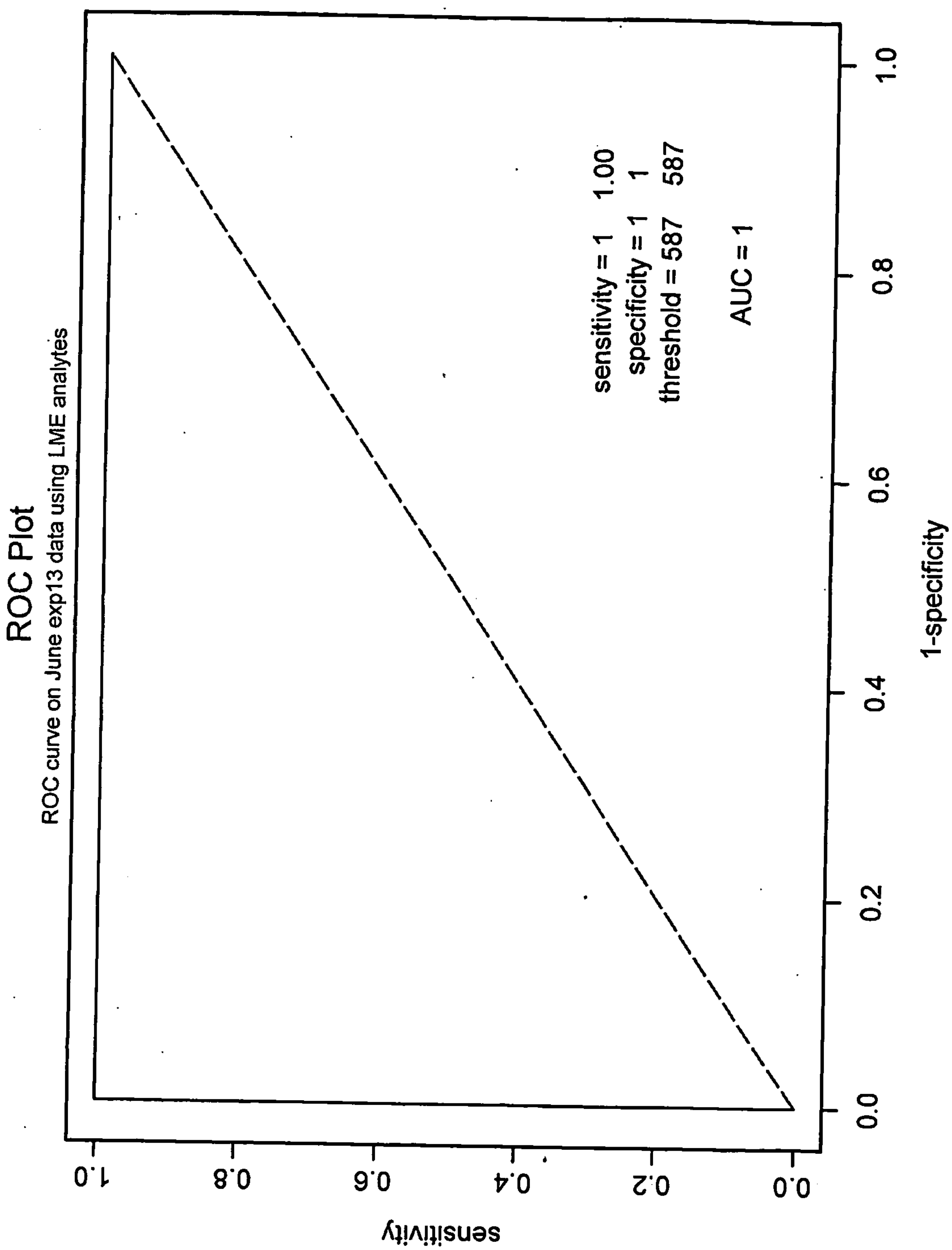

scores of June exp7 animals using LME analytes
scores
500
600
700
800
900
1000
SURVIVED
DOOMED
LPS
Final
category

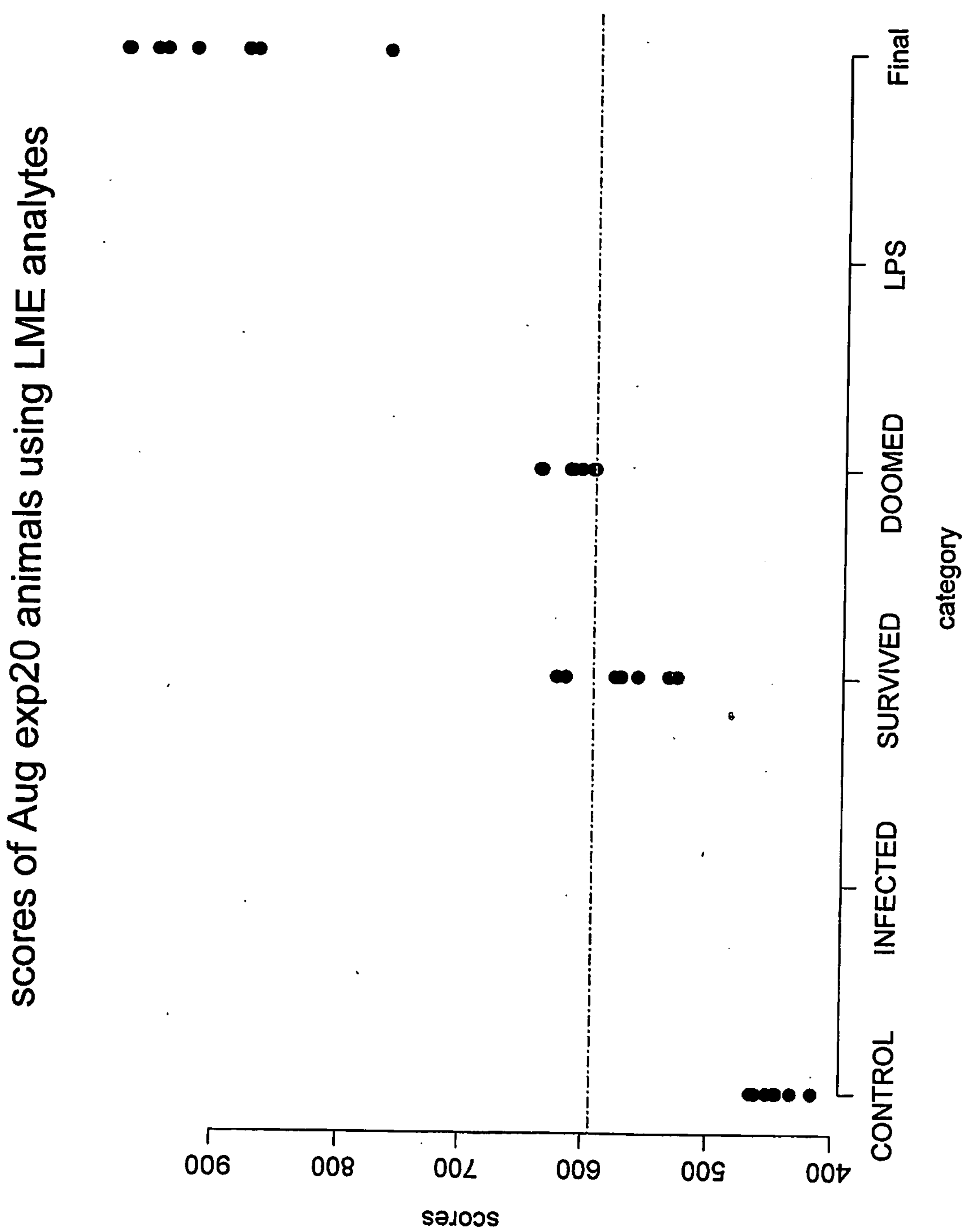

scores of June exp7 animals using LME analytes
scores
1000
900
800
700
600
500
SURVIVED
DOOMED
FINAL
category

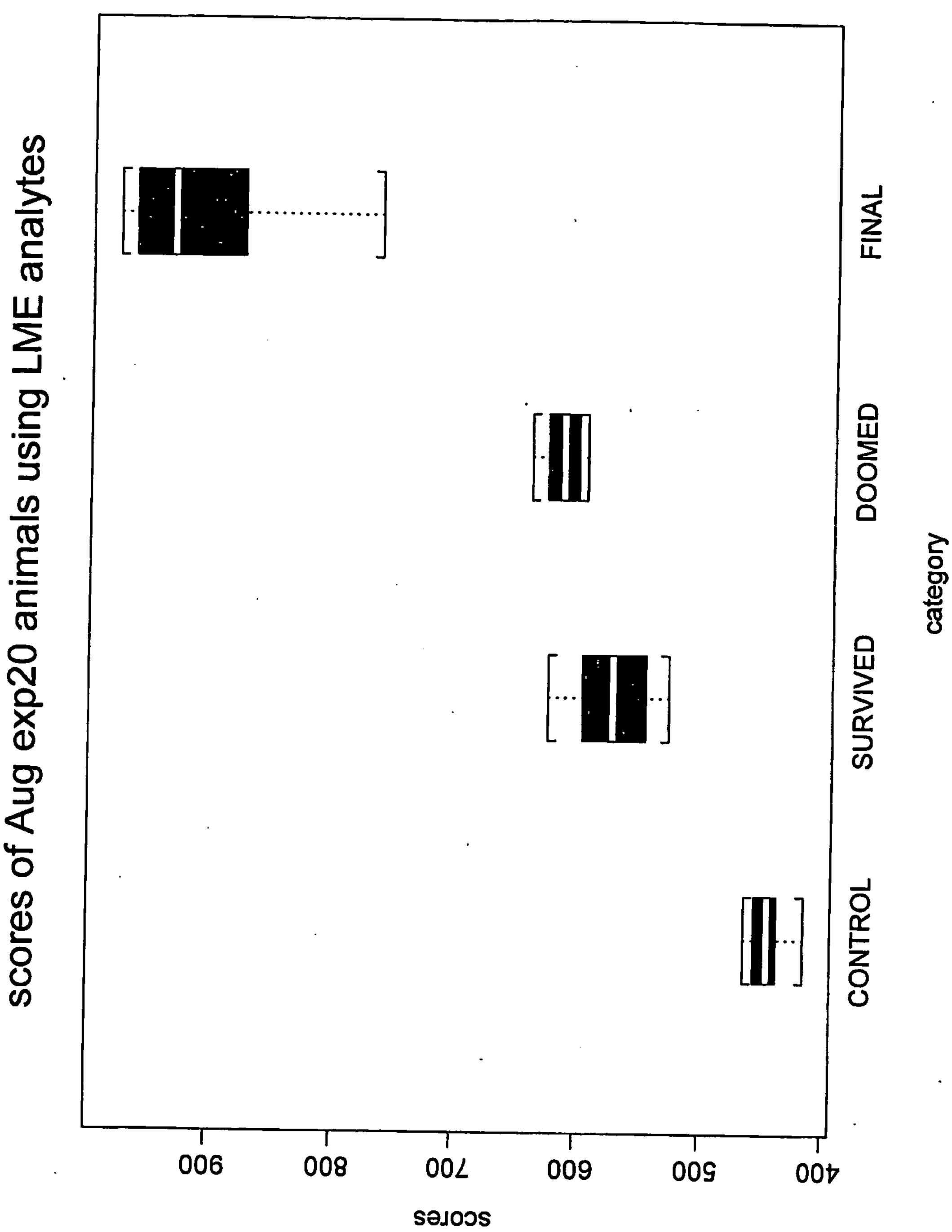

ROC Plot
ROC curve on June exp7 data using LME analytes
sensitivity = 1 1.00
specificity = 0.75 0.75
threshold = 628.67 628.67
AUC = 0.875
sensitivity
0.0
0.2
0.4
0.6
0.8
1.0
1-specificity
0.0
0.2
0.4
0.6
0.8
1.0

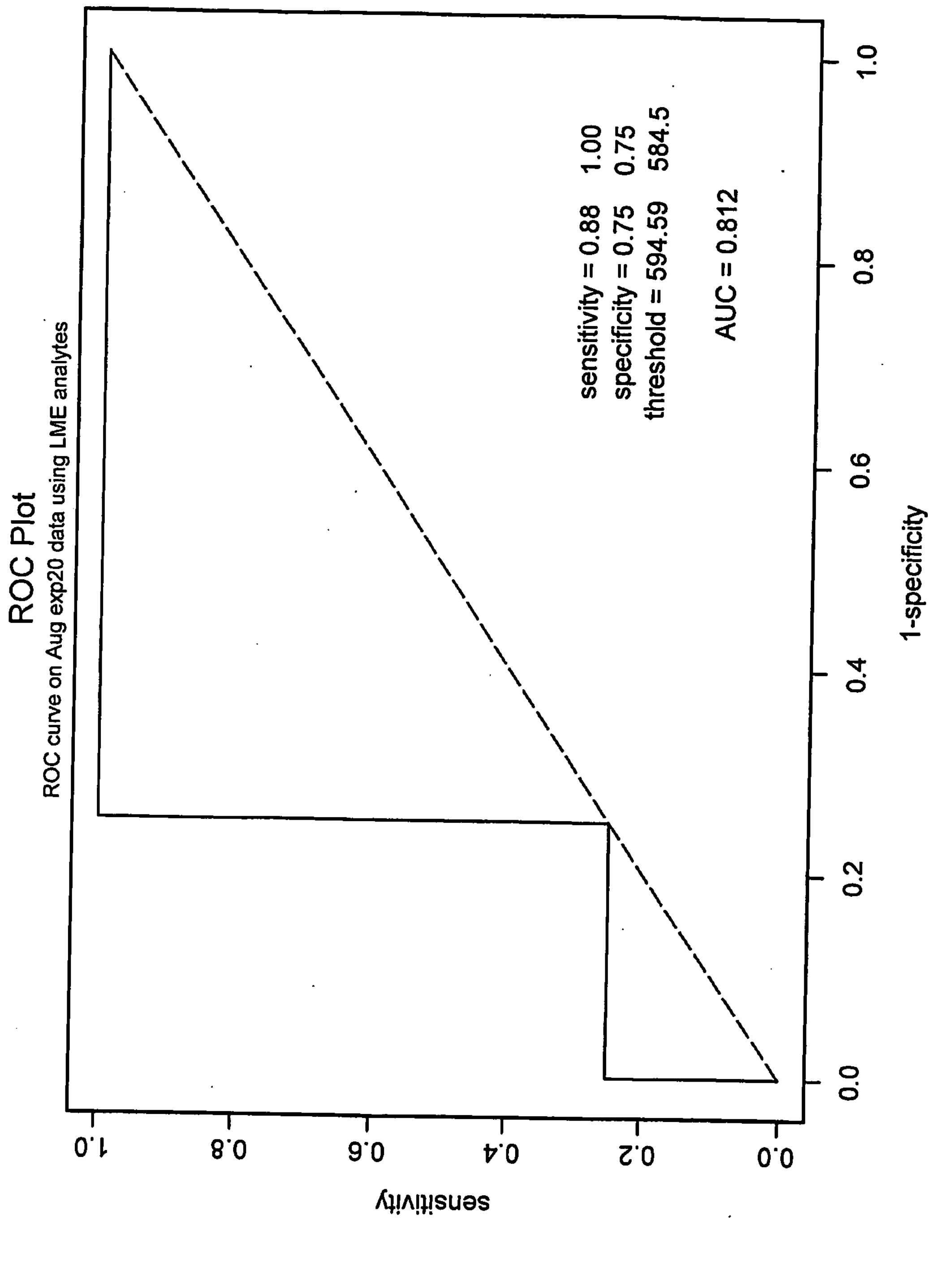

scores of June exp13 animals using LME analytes
scores
640
620
600
580
category
SURVIVED
DOOMED

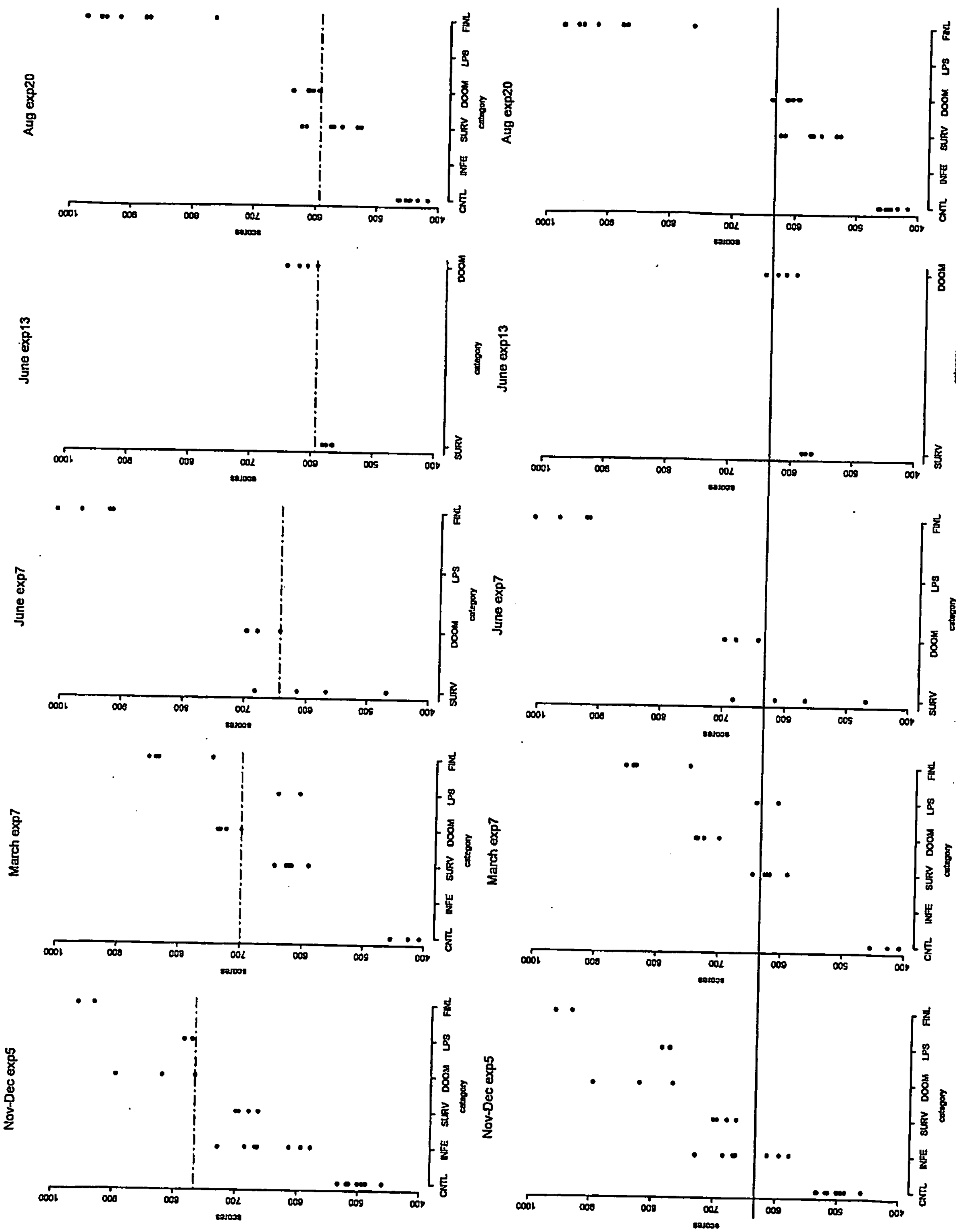

scores of June exp13 animals using LME analytes
scores
640
620
600
580
SURVIVED
DOOMED
category

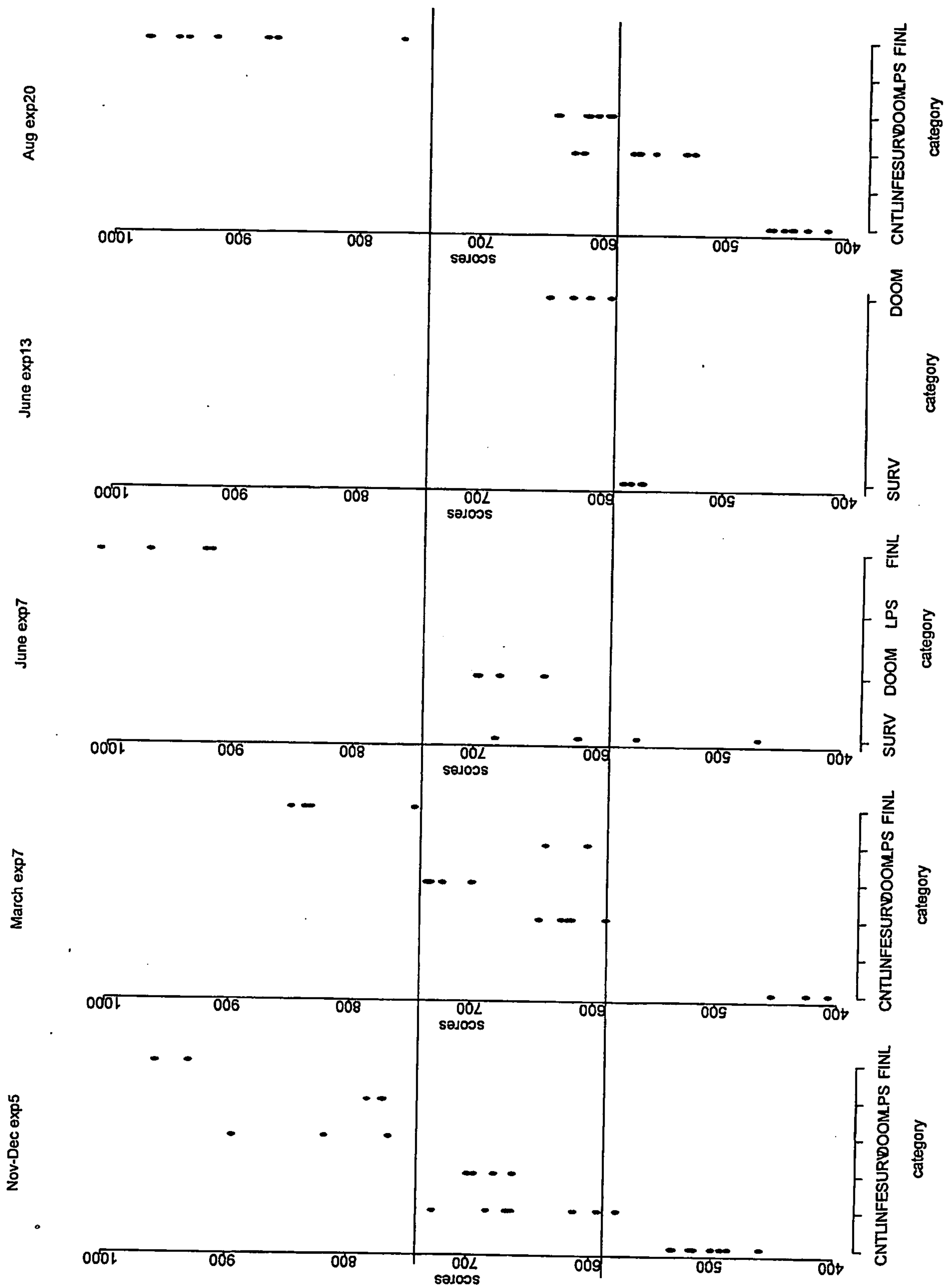

ROC Plot
ROC curve on June exp13 data using LME analytes
sensitivity = 1 1.00
specificity = 1 1
threshold = 587 587
AUC = 1
1-specificity
sensitivity
0.0
0.2
0.4
0.6
0.8
1.0


scores of Aug exp20 animals using LME analytes
scores
400
500
600
700
800
900
CONTROL
INFECTED
SURVIVED
DOOMED
LPS
Final
category

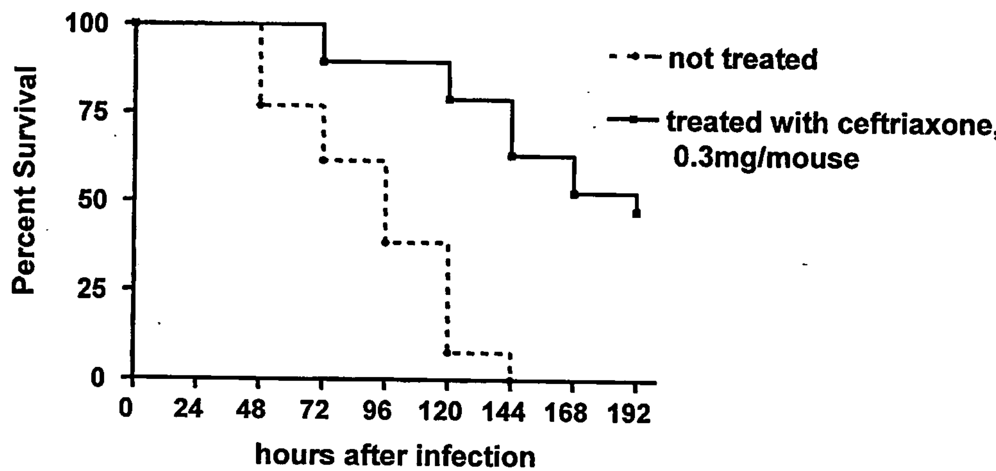

scores of Aug exp20 animals using LME analytes
CONTROL
SURVIVED
DOOMED
FINAL
category
scores
400
500
600
700
800
900


ROC Plot
ROC curve on Aug exp20 data using LME analytes
sensitivity = 0.88 1.00
specificity = 0.75 0.75
threshold = 594.59 584.5
AUC = 0.812
1-specificity
sensitivity
0.0
0.2
0.4
0.6
0.8
1.0


Aug exp20
June exp13
June exp7
March exp7
Nov-Dec exp5
scores
category
CNTL
INFE
SURV
DOOM
LPS
FINL
Aug exp20
June exp13
June exp7
March exp7
Nov-Dec exp5


Aug exp20
June exp13
June exp7
March exp7
Nov-Dec exp5
scores
category
CNTLINFESURVDOOMLPS FINL
SURV DOOM
SURV DOOM LPS FINL
400 500 600 700 800 900 1000

APPENDIX C



not treated
treated with ceftriaxone, 0.3mg/mouse
Percent Survival
100
75
50
25
0
0 24 48 72 96 120 144 168 192
hours after infection

APPENDIX D

hour	description	animal	Bact.counts	Apolipoprotein	C Reactive Prot	EGF	Endothelin-1	Eotaxin	Factor VII	FGF-9	FGF-basic
0	CONTROL	1	0.00E+00	268.00	1.76	4.00	7.94	1070.00	0.40	0.08	0.29
0	CONTROL	2	0.00E+00	285.00	1.81	15.50	22.20	1060.00	1.15	0.08	0.46
0	CONTROL	3	0.00E+00	152.00	0.71	21.90	23.80	1860.00	1.15	0.08	0.65
0	CONTROL	4	0.00E+00	173.00	0.76	35.00	20.50	3200.00	0.29	0.08	0.65
0	XR.CONTROL	6	0.00E+00	288.00	2.36	8.48	15.30	1020.00	0.92	0.08	0.79
0	XR.CONTROL	7	0.00E+00	186.00	1.39	4.43	20.50	1930.00	1.20	0.08	0.65
0	XR.CONTROL	8	0.00E+00	171.00	0.80	12.60	13.30	3360.00	0.97	0.08	0.51
0	XR.CONTROL	9	0.00E+00	226.00	1.31	8.96	9.12	2450.00	0.74	0.08	0.16
0	CONTROL	10	0.00E+00	235.00	1.65	18.60	20.50	1540.00	0.97	0.08	0.16
0	CONTROL	11	0.00E+00	238.00	1.47	17.00	18.00	2570.00	1.20	0.08	0.56
0	CONTROL	12	0.00E+00	208.00	1.43	7.55	16.20	1430.00	0.63	0.08	0.51
0	CONTROL	13	0.00E+00	243.00	1.83	9.92	12.30	1780.00	0.74	0.08	0.41
0	XR.CONTROL	14	0.00E+00	209.00	1.13	15.70	17.10	2710.00	1.09	0.08	0.51
0	XR.CONTROL	15	0.00E+00	188.00	1.43	13.40	15.30	2960.00	0.97	0.08	0.16
0	XR.CONTROL	16	0.00E+00	175.00	1.49	11.90	17.10	3010.00	0.63	0.08	0.35
0	XR.CONTROL	17	0.00E+00	154.00	0.84	3.37	9.12	4520.00	0.29	0.08	0.16
4	4-INFECTED	18	0.00E+00	202.00	1.45	8.96	22.20	1180.00	0.52	0.08	0.41
4	4-INFECTED	19	0.00E+00	230.00	1.67	18.60	28.30	982.00	1.61	0.13	0.61
4	4-INFECTED	20	0.00E+00	230.00	1.74	28.90	12.30	1210.00	0.92	0.08	0.70
4	4-INFECTED	21	0.00E+00	190.00	2.45	13.40	22.20	1010.00	0.63	0.34	0.16
4	4-INFECTED	22	0.00E+00	143.00	0.79	9.44	22.20	3910.00	1.20	0.08	0.56
4	4-INFECTED	23	0.00E+00	136.00	0.86	11.90	22.20	4380.00	0.74	0.57	0.41
4	4-XR-INFECTED	26	0.00E+00	245.00	1.85	4.00	6.68	2400.00	0.63	0.08	0.16
4	4-XR-INFECTED	27	0.00E+00	235.00	1.48	6.18	11.30	3530.00	0.40	0.57	0.29
4	4-XR-INFECTED	28	0.00E+00	211.00	0.88	21.80	19.70	2820.00	1.61	0.46	1.15
4	4-XR-INFECTED	29	0.00E+00	177.00	0.93	13.10	11.30	3930.00	0.97	1.07	0.29
4	4-XR-INFECTED	30	0.00E+00	209.00	1.25	4.00	17.10	3450.00	0.29	0.08	0.16
10	10-XR-INFECTED	31	0.00E+00	227.00	1.68	18.10	13.30	1180.00	0.69	1.21	0.41
10	10-XR-INFECTED	32	0.00E+00	187.00	1.33	2.36	15.30	2510.00	0.69	0.21	0.16
10	10-XR-INFECTED	33	0.00E+00	232.00	1.78	14.40	18.90	2130.00	0.74	1.86	0.16
10	10-XR-INFECTED	34	0.00E+00	154.00	0.77	10.70	11.30	4790.00	0.63	1.53	0.29
10	10-XR-INFECTED	36	7.00E+00	295.00	2.12	4.64	23.80	1030.00	1.43	0.57	0.41
10	10-INFECTED	37	0.00E+00	210.00	1.50	14.90	17.10	2760.00	0.57	1.16	0.29
10	10-INFECTED	39	0.00E+00	207.00	1.95	8.72	5.29	1080.00	0.52	0.08	0.51
10	10-INFECTED	40	0.00E+00	167.00	0.87	8.48	15.30	3340.00	0.74	0.62	0.35
10	10-INFECTED	41	0.00E+00	195.00	1.83	12.40	22.20	692.00	1.38	0.08	0.79
10	10-INFECTED	42	0.00E+00	177.00	1.60	16.20	13.30	1740.00	0.40	0.08	0.16
24	24-INFECTED	43	1.00E+03	209.00	1.78	13.10	20.50	1990.00	1.09	1.12	0.93
24	24-INFECTED	44	0.00E+00	277.00	2.33	1.66	20.50	913.00	1.43	0.08	0.41
24	24-INFECTED	45	0.00E+00	130.00	1.19	19.70	26.80	2710.00	0.97	0.08	0.70
24	24-INFECTED	46	0.00E+00	196.00	2.61	5.29	18.90	1020.00	1.78	0.08	1.08
24	24-INFECTED	47	0.00E+00	198.00	1.48	20.80	17.10	3120.00	1.09	0.08	0.61
24	24-XR-INFECTED	48	0.00E+00	208.00	1.85	3.79	15.30	2710.00	0.74	0.08	0.16
24	24-XR-INFECTED	49	0.00E+00	240.00	2.28	7.09	20.50	1720.00	1.20	0.08	0.29
24	24-XR-INFECTED	50	0.00E+00	280.00	2.40	6.18	11.30	1710.00	0.74	0.08	0.29
24	24-XR-INFECTED	51	0.00E+00	267.00	1.77	5.51	11.30	3150.00	0.74	0.34	0.51

24	24-XR-INFECTED	52	0.00E+00	189.00	0.58	15.50	17.10	5654.00	0.80	0.28	0.16
24	24-XR-INFECTED	53	TNTC	140.00	0.58	7.09	18.90	5654.00	0.74	0.97	1.11
48	48-INFECTED	54	1.40E+01	212.00	1.77	1.56	11.30	1650.00	0.40	0.08	1.11
48	48-INFECTED	55	1.00E+03	97.80	0.70	4.86	23.80	1970.00	1.43	5.03	0.89
48	48-INFECTED	56	2.00E+01	136.00	0.64	8.96	13.30	3640.00	0.86	0.08	0.29
48	48-INFECTED	57	1.25E+02	122.00	0.45	16.80	9.12	3760.00	1.15	0.21	0.46
48	48-INFECTED	58	6.00E+00	130.00	0.60	20.50	15.30	3300.00	0.40	0.57	0.51
48	48-XR-INFECTED	59	2.00E+02	152.00	0.56	17.60	15.30	3470.00	1.09	0.46	0.56
48	48-XR-INFECTED	60	1.00E+00	139.00	1.10	5.51	15.30	4010.00	0.57	0.21	0.35
48	48-XR-INFECTED	61	3.00E+00	187.00	1.49	9.44	6.68	3080.00	0.40	0.08	0.16
48	48-XR-INFECTED	62	1.00E+00	179.00	1.12	9.92	16.20	3960.00	0.86	0.97	0.41
48	48-XR-INFECTED	63	1.00E+00	160.00	1.17	19.40	5.29	4450.00	0.74	0.40	0.16
72	72-INFECTED	84	0.00E+00	132.00	0.40	31.10	24.20	4290.00	1.47	0.30	0.93
72	72-INFECTED	85	0.00E+00	181.00	0.54	52.10	53.30	4020.00	3.63	0.08	1.33
72	72-INFECTED	86	0.00E+00	207.00	1.86	13.00	20.40	770.00	0.09	0.12	0.63
72	72-INFECTED	87	0.00E+00	144.00	1.09	27.80	16.00	3340.00	1.26	0.08	0.63
72	72-XR-INFECTED	88	0.00E+00	206.00	1.74	20.40	16.00	1480.00	0.09	0.20	0.63
72	72-XR-INFECTED	89	0.00E+00	144.00	1.02	19.40	18.70	4350.00	0.77	0.30	0.55
72	72-XR-INFECTED	90	6×10^8	114.00	0.87	17.30	33.20	4590.00	1.02	4.66	0.67
72	72-XR-INFECTED	91	2×10^4	132.00	1.47	25.80	17.90	3490.00	0.08	1.25	1.51
72	72-XR-INFECTED	92	0.00E+00	159.00	1.33	22.00	17.90	2970.00	0.31	0.08	0.63
96	96-INFECTED	93	0.00E+00	128.00	0.85	20.40	5.76	3810.00	0.77	0.33	0.67
96	96-INFECTED	94	0.00E+00	131.00	1.08	22.80	18.70	2260.00	0.77	0.08	0.70
96	96-INFECTED	95	0.00E+00	155.00	1.31	22.00	18.00	1860.00	0.31	0.08	0.48
96	96-INFECTED	96	0.00E+00	165.00	1.35	9.32	20.40	1600.00	0.31	0.08	0.70
96	96-INFECTED	97	0.00E+00	151.00	1.53	10.90	5.76	2020.00	0.48	0.08	0.70
96	96-XR-INFECTED	98	2.00E+08	104.00	0.97	6.40	17.90	5320.00	0.09	5.97	0.93
96	96-XR-INFECTED	99	2.00E+03	116.00	0.72	19.90	17.80	3510.00	0.31	0.82	0.74
96	96-XR-INFECTED	100	0.00E+00	130.00	1.21	22.60	14.00	3060.00	0.63	0.48	0.78
96	96-XR-INFECTED	102	0.00E+00	174.00	1.69	21.00	12.90	1860.00	0.09	0.08	0.48
96	96-XR-INFECTED	103	1.30E+07	71.50	0.67	0.63	11.70	5290.00	0.31	4.91	0.74
96	96-XR-INFECTED	104	2.00E+06	144.00	2.10	9.32	11.70	1310.00	0.70	2.97	0.85
96	96-XR-INFECTED-FINAL	10F	1.20E+09	56.60	0.28	1.50	24.20	4230.00	0.98	5.90	0.70
96	96-XR-INFECTED-FINAL	11F	2.20E+09	65.10	0.45	3.66	5.76	5654.00	0.56	5.88	0.59
48	48-XR-INFECTED-FINAL	1d	2.60E+09	87.90	0.05	3.17	15.30	4300.00	0.92	8.10	0.41
48	48-XR-INFECTED-FINAL	1F	7.00E+07	48.20	0.21	3.58	13.30	5640.00	0.97	7.58	0.70
48	48-XR-INFECTED-FINAL	2d	2.20E+09	218.00	0.01	5.28	27.50	2020.00	0.80	8.52	0.70
48	48-XR-INFECTED-FINAL	2F	5.00E+08	102.00	0.81	0.74	38.90	4960.00	1.03	9.80	0.29
48	48 INFECTED-FINAL	3d	TNTC	237.00	0.03	8.48	16.20	252.00	0.92	5.97	4.03
48	48-XR-INFECTED-FINAL	3F	3.00E+06	70.70	0.01	11.80	11.30	5654.00	1.66	6.68	0.79
48	48-XR-INFECTED-FINAL	4F	8.00E+08	70.70	0.17	7.76	14.80	5654.00	1.06	6.80	1.03
72	72-XR-INFECTED-FINAL	5d	1.20E+10	31.90	0.01	15.10	21.20	337.00	1.26	4.10	2.49
48	48-XR-INFECTED-FINAL	5F	1.00E+08	48.10	0.30	6.40	5.76	5654.00	0.31	5.35	0.67
72	72-XR-INFECTED-FINAL	6F	8.00E+08	116.00	0.17	19.40	24.20	4480.00	1.42	4.99	0.89
72	72-XR-INFECTED-FINAL	7F	6.00E+08	66.10	0.35	9.85	31.40	5640.00	1.26	6.70	0.78
72	72-XR-INFECTED-FINAL	8F	6.00E+08	78.60	0.75	7.20	36.50	3670.00	0.31	4.76	0.81
96	96-XR-INFECTED-FINAL	9F	5.00E+08	67.10	0.36	17.30	29.60	3400.00	0.96	5.39	0.48

Fibrinogen	GCP-2 / LIX	GM-CSF	Growth Hormon	GST	Haptoglobin	IFN-g	IgA	IL-10	IL-11	IL-12p70	IL-17	IL-18
4480.00	0.36	2.50	0.01	0.18	44.80	2.03	194.00	97.30	72.30	0.10	0.00	0.73
4390.00	1.03	3.99	0.05	0.43	47.40	2.03	160.00	134.00	142.00	0.10	0.00	1.08
2620.00	3.62	4.76	0.04	1.52	15.60	2.03	151.00	276.00	36.20	0.14	0.00	0.88
1670.00	13.60	5.52	0.03	0.57	26.10	2.03	191.00	179.00	72.30	0.23	0.02	1.57
3810.00	2.36	7.00	0.04	0.50	18.30	2.03	126.00	164.00	44.50	0.10	0.00	1.22
3080.00	0.61	1.62	0.12	0.87	12.20	2.03	113.00	17.00	39.00	0.55	0.01	0.90
2540.00	1.54	5.52	0.01	1.27	14.40	2.03	100.00	127.00	55.60	0.10	0.00	0.91
3770.00	0.22	3.26	0.01	0.94	14.80	2.03	144.00	82.40	44.50	0.10	0.00	0.84
3980.00	1.03	1.29	0.01	0.87	58.50	2.03	118.00	82.40	39.00	0.10	0.00	0.74
3530.00	0.87	7.00	0.03	0.57	41.20	10.50	123.00	40.30	66.70	0.55	0.01	1.00
4040.00	1.71	7.00	0.01	0.87	64.00	14.60	132.00	89.90	89.30	1.00	0.02	0.97
3880.00	0.53	12.60	0.01	0.30	24.50	2.03	145.00	74.90	86.40	0.14	0.00	0.98
2750.00	1.03	5.52	0.06	1.02	42.10	2.03	93.00	74.90	147.00	0.14	0.00	0.84
2720.00	0.87	3.99	0.03	1.87	31.40	9.16	99.20	101.00	9.15	0.75	0.00	0.85
4370.00	0.70	14.00	0.01	0.87	14.50	10.50	109.00	59.80	9.15	0.10	0.02	0.91
3400.00	2.04	1.29	0.01	0.30	36.40	2.03	91.20	105.00	33.50	0.10	0.00	0.98
3870.00	1.71	3.26	0.01	0.87	33.60	2.03	124.00	146.00	75.10	0.10	0.01	0.90
5250.00	3.47	1.29	0.10	2.59	58.90	2.03	122.00	194.00	61.10	0.44	0.04	1.16
4670.00	1.03	7.00	0.01	1.02	46.80	2.03	151.00	120.00	63.90	0.55	0.00	1.04
11400.00	1.45	11.90	0.01	0.64	83.70	14.60	150.00	201.00	196.00	0.10	0.06	1.02
3240.00	5.51	4.76	0.06	1.27	34.90	2.03	117.00	142.00	77.90	0.55	0.01	1.14
3010.00	3.47	14.00	0.04	1.10	30.10	16.00	89.20	186.00	97.90	0.75	0.01	0.98
5170.00	1.20	3.99	0.01	0.18	65.90	2.03	104.00	97.30	133.00	0.44	0.00	1.00
4360.00	2.36	6.27	0.01	0.43	45.00	2.03	103.00	316.00	142.00	0.10	0.03	0.90
3570.00	2.52	7.00	0.02	1.10	43.80	5.09	99.70	327.00	112.00	0.66	0.02	1.01
3150.00	1.87	15.40	0.07	1.10	36.40	5.09	87.40	246.00	124.00	0.84	0.00	1.01
3390.00	2.20	5.52	0.01	0.13	50.60	2.03	98.40	172.00	88.40	0.31	0.01	0.95
6000.00	2.52	5.52	0.05	0.07	53.10	6.46	150.00	209.00	142.00	0.31	0.04	1.08
6070.00	2.04	4.76	0.01	0.43	63.10	2.03	112.00	59.80	112.00	0.44	0.02	1.22
7080.00	4.66	3.26	0.01	0.30	63.90	21.60	155.00	348.00	285.00	0.61	0.02	1.52
5880.00	7.11	7.00	0.01	1.10	60.60	7.81	123.00	510.00	319.00	0.14	0.01	1.13
6140.00	2.04	5.52	0.01	1.35	60.70	7.81	136.00	235.00	118.00	0.10	0.03	1.23
7240.00	4.07	19.60	0.01	0.43	84.60	33.00	137.00	283.00	142.00	1.00	0.09	1.14
6420.00	3.47	13.30	0.01	0.36	71.10	7.81	131.00	134.00	44.50	0.44	0.00	1.01
6070.00	10.00	14.70	0.04	1.52	68.70	10.50	147.00	254.00	104.00	0.50	0.04	1.19
4800.00	0.70	3.99	0.09	1.02	61.00	2.03	199.00	149.00	75.10	0.44	0.02	1.05
4800.00	5.92	2.50	0.01	0.36	51.80	7.81	122.00	180.00	50.00	0.38	0.03	1.12
12600.00	6.08	16.80	0.06	1.19	65.70	14.60	197.00	466.00	162.00	0.92	0.11	1.52
14500.00	2.68	14.00	0.16	1.35	73.40	2.03	221.00	44.30	9.15	0.44	0.01	1.08
8740.00	5.65	5.52	0.06	0.36	65.10	5.09	171.00	44.30	50.00	0.84	0.02	1.14
8840.00	7.24	7.00	0.09	0.30	74.60	2.03	149.00	82.40	89.30	0.10	0.00	1.27
3690.00	7.24	1.29	0.01	0.30	77.20	2.03	171.00	17.00	22.30	0.31	0.00	1.22
7040.00	2.68	2.50	0.02	0.07	73.00	2.03	142.00	224.00	168.00	0.31	0.04	1.21
11800.00	1.37	8.43	0.03	1.19	66.20	11.90	154.00	160.00	44.50	0.23	0.04	1.17
9740.00	0.70	9.85	0.01	0.24	84.80	10.50	146.00	105.00	25.10	0.44	0.00	0.98
12400.00	0.87	8.43	0.06	0.87	77.30	13.20	149.00	89.90	44.50	0.10	0.07	0.87

6640.00	0.28	11.30	0.01	0.36	69.80	7.81	72.40	105.00	142.00	0.44	0.00	0.87
8840.00	3.00	14.00	0.05	0.64	75.10	34.50	130.00	348.00	202.00	0.31	0.08	1.24
8690.00	2.52	1.29	0.07	2.68	77.90	2.03	176.00	134.00	52.80	0.14	0.02	1.16
13900.00	16.20	39.20	0.06	0.07	63.80	85.10	336.00	2200.00	363.00	1.59	0.22	1.44
8050.00	6.79	2.50	0.01	0.50	67.70	10.50	126.00	17.00	77.90	0.14	0.00	1.14
5930.00	7.62	5.52	0.01	0.07	69.80	2.03	98.20	67.40	41.80	0.44	0.00	0.98
5840.00	3.54	13.30	0.01	0.07	65.60	5.09	87.70	17.00	92.10	0.55	0.00	0.77
6500.00	5.72	11.90	0.02	1.10	43.60	25.80	66.00	231.00	183.00	0.70	0.02	1.14
9160.00	4.07	7.00	0.04	0.87	76.80	16.00	94.60	134.00	118.00	0.55	0.06	0.87
8840.00	3.16	3.99	0.01	0.07	70.90	2.03	144.00	74.90	104.00	0.31	0.04	0.61
10200.00	3.39	20.90	0.01	0.07	76.90	11.90	116.00	134.00	101.00	0.55	0.02	1.19
6450.00	1.29	6.27	0.01	1.27	65.30	36.00	138.00	239.00	348.00	0.66	0.05	1.12
2920.00	1.56	4.14	0.06	0.57	59.80	7.11	139.00	93.50	151.00	0.10	0.01	0.69
2490.00	1.94	4.43	0.11	0.07	83.70	29.60	113.00	722.00	168.00	0.29	0.00	0.94
3510.00	1.40	7.83	0.01	1.08	51.60	12.10	218.00	64.50	47.80	0.30	0.01	0.41
3310.00	1.72	2.46	0.01	0.39	88.70	2.03	146.00	17.00	71.00	0.16	0.01	0.69
7390.00	1.87	5.47	0.01	0.22	82.20	17.60	187.00	57.30	35.90	0.44	0.00	0.67
6270.00	3.29	6.87	0.01	0.07	71.50	29.40	177.00	123.00	122.00	0.10	0.02	0.90
7560.00	17.90	30.40	0.01	0.57	74.20	127.00	161.00	3940.00	594.00	2.21	0.62	1.26
7470.00	13.70	15.00	0.01	0.45	76.00	24.50	296.00	652.00	352.00	0.64	0.09	1.20
8900.00	1.08	7.83	0.01	0.39	78.70	28.10	199.00	86.20	169.00	0.22	0.02	0.72
5610.00	2.18	5.47	0.03	1.21	65.80	7.11	80.70	53.70	108.00	0.10	0.02	0.67
5310.00	1.87	3.71	0.01	0.15	76.20	13.20	113.00	50.20	65.30	0.20	0.03	0.81
4240.00	1.64	7.83	0.02	0.89	69.60	9.06	154.00	17.00	82.20	0.57	0.02	0.72
6500.00	1.08	4.14	0.01	0.07	65.80	19.80	152.00	64.50	47.80	0.30	0.00	0.65
5960.00	0.92	2.46	0.02	0.07	81.40	17.60	184.00	17.00	38.30	0.30	0.01	0.68
7800.00	23.60	32.60	0.01	0.07	65.40	166.00	66.00	5340.00	617.00	2.25	0.82	0.87
8870.00	10.20	5.93	0.01	1.01	70.00	23.30	130.00	303.00	284.00	0.64	0.02	1.00
6680.00	4.17	7.83	0.03	0.07	74.90	19.80	181.00	123.00	71.00	0.10	0.04	0.98
6760.00	0.22	1.29	0.01	0.95	73.30	6.17	173.00	64.50	52.70	0.30	0.00	0.57
8020.00	17.80	36.00	0.01	0.57	56.40	108.00	78.10	4580.00	549.00	2.13	0.38	1.14
8150.00	8.33	15.00	0.04	1.34	83.50	67.90	165.00	2130.00	267.00	1.31	0.17	1.16
7830.00	27.80	145.00	0.01	0.82	54.10	199.00	65.60	5130.00	739.00	3.08	0.77	2.25
9180.00	17.40	45.10	0.01	0.07	55.50	111.00	77.70	4300.00	601.00	2.13	0.32	1.10
4930.00	61.80	520.00	0.01	0.87	57.30	207.00	38.70	8400.00	1710.00	3.41	0.75	1.28
6000.00	34.10	78.50	0.01	0.30	51.90	137.00	51.10	3890.00	776.00	2.87	0.66	1.37
2010.00	49.70	141.00	0.01	0.79	48.00	201.00	64.00	8650.00	953.00	3.35	0.77	1.38
12700.00	28.50	76.60	0.03	0.57	62.10	204.00	57.00	6070.00	853.00	3.82	0.76	1.34
333.00	18.20	125.00	0.07	2.87	29.20	159.00	15.70	5810.00	569.00	2.23	0.52	1.57
5820.00	19.50	54.10	0.03	0.87	54.50	140.00	32.90	2900.00	517.00	1.92	0.34	1.46
11200.00	43.60	98.00	0.07	1.62	76.80	227.00	112.00	4980.00	1120.00	3.77	0.91	1.69
227.00	24.00	356.00	0.01	1.34	31.40	151.00	14.80	5260.00	511.00	2.00	0.41	1.74
9960.00	25.70	106.00	0.01	0.70	55.20	149.00	109.00	4010.00	791.00	2.27	0.56	1.08
3120.00	21.40	87.50	0.03	0.45	44.10	209.00	76.20	5360.00	838.00	2.56	0.60	1.97
8790.00	37.80	120.00	0.01	1.34	72.30	204.00	108.00	5930.00	774.00	3.11	0.84	3.80
9870.00	17.20	31.50	0.02	0.07	73.30	137.00	81.80	4770.00	643.00	2.54	0.58	1.38
6380.00	18.60	105.00	0.06	0.70	54.20	196.00	57.20	4960.00	701.00	2.81	0.72	4.73

IL-1alpha	IL-1beta	IL-2	IL-3	IL-4	IL-5	IL-6	IL-7	Insulin	IP-10	KC / GROalpha	Leptin	LIF
1.53	0.12	6.88	1.36	11.70	0.04	7.81	0.01	0.88	6.26	0.04	2.66	39.60
63.20	0.24	17.80	1.36	11.70	0.06	7.81	0.04	3.06	20.00	0.04	2.15	141.00
1.53	0.35	6.88	10.80	11.70	0.10	7.81	0.04	3.10	42.20	0.04	2.98	116.00
45.40	0.40	7.85	1.95	11.70	0.12	12.90	0.08	2.80	38.60	0.04	2.85	53.70
75.00	0.10	46.60	2.48	37.70	0.12	9.86	0.01	2.48	20.00	0.04	1.64	116.00
10.70	0.09	46.60	1.36	82.30	0.08	7.81	0.01	0.69	33.40	0.04	1.10	70.80
2.75	0.17	6.88	1.36	11.70	0.07	7.81	0.06	1.28	26.70	0.04	0.87	84.00
1.53	0.06	6.88	1.36	11.70	0.02	7.81	0.01	0.21	13.50	0.04	1.37	50.30
28.30	0.09	17.80	2.94	11.70	0.01	7.81	0.01	0.79	20.00	0.04	0.63	103.00
30.70	0.12	46.60	7.07	86.70	0.06	7.81	0.01	3.58	40.40	0.04	2.13	80.70
1.53	0.22	72.20	6.61	48.50	0.07	14.30	0.01	2.80	54.70	0.04	0.96	77.40
8.70	0.09	17.80	1.36	11.70	0.05	11.50	0.03	0.21	26.70	0.04	1.83	50.30
1.53	0.14	6.88	1.36	11.70	0.05	7.81	0.01	2.02	30.00	0.04	0.71	87.30
18.10	0.14	6.88	2.48	58.70	0.04	7.81	0.01	1.28	26.70	0.04	0.97	50.30
5.75	0.06	6.88	1.36	37.70	0.05	7.81	0.01	0.21	40.40	0.04	0.46	64.00
6.73	0.14	6.88	1.36	11.70	0.05	7.81	0.01	0.42	12.10	0.04	0.63	36.00
52.90	0.19	17.80	1.36	19.30	0.04	199.00	0.02	0.93	258.00	1.45	0.86	97.00
94.80	0.19	72.20	4.33	19.30	0.10	133.00	0.01	1.02	185.00	1.35	2.04	116.00
17.00	0.06	72.20	1.36	31.90	0.05	109.00	0.04	0.21	76.70	0.61	2.81	80.70
52.90	0.21	96.60	23.10	25.80	0.10	644.00	0.01	0.21	596.00	1.41	0.66	57.20
65.80	0.29	46.60	2.94	19.30	0.04	105.00	0.06	1.97	106.00	2.09	1.89	103.00
124.00	0.24	32.90	4.33	58.70	0.05	142.00	0.09	0.42	78.50	2.75	3.98	103.00
34.30	0.21	6.88	7.07	11.70	0.02	160.00	0.01	0.42	463.00	1.87	0.41	24.80
73.70	0.14	72.20	24.60	25.80	0.01	469.00	0.07	0.21	435.00	7.56	0.54	20.90
28.30	0.17	25.70	14.70	58.70	0.04	245.00	0.01	1.17	300.00	4.00	0.61	64.00
65.80	0.32	65.90	18.60	11.70	0.06	199.00	0.02	0.21	214.00	7.30	0.61	103.00
46.60	0.12	46.60	12.20	48.50	0.01	176.00	0.07	0.21	155.00	5.20	1.10	28.60
88.20	0.37	6.88	12.70	48.50	0.10	251.00	0.07	0.21	533.00	4.56	2.02	103.00
26.00	0.12	17.80	9.39	37.70	0.10	160.00	0.05	0.59	110.00	5.62	1.47	64.00
72.40	0.29	59.60	33.20	37.70	0.08	668.00	0.04	0.21	689.00	11.90	1.34	57.20
185.00	0.21	84.50	37.80	25.80	0.06	206.00	0.22	0.59	334.00	8.81	0.58	43.20
42.90	0.42	59.60	13.70	31.90	0.07	251.00	0.01	1.59	438.00	2.57	0.78	97.00
33.10	0.26	72.20	28.10	48.50	0.07	582.00	0.15	0.66	151.00	3.00	1.84	67.20
52.90	0.24	6.88	14.70	11.70	0.10	502.00	0.07	3.02	95.30	1.68	1.87	50.30
46.60	0.28	7.85	26.10	68.40	0.10	491.00	0.03	1.88	56.50	5.80	0.88	50.30
35.50	0.21	6.88	7.07	31.90	0.11	109.00	0.06	5.17	322.00	0.48	3.90	135.00
78.90	0.19	25.70	15.60	77.70	0.06	563.00	0.05	1.07	65.60	5.02	2.13	77.40
104.00	0.28	84.50	46.40	86.70	0.12	538.00	0.09	1.17	329.00	2.27	0.77	64.00
21.40	0.14	6.88	10.80	19.30	0.14	67.30	0.01	2.84	114.00	0.04	1.15	64.00
1.53	0.30	65.90	9.39	37.70	0.13	41.60	0.05	2.30	23.30	1.51	1.07	116.00
26.00	0.34	6.88	9.86	31.90	0.08	225.00	0.01	0.79	80.40	1.61	0.45	77.40
196.00	0.21	6.88	7.07	11.70	0.12	11.50	0.04	1.39	40.40	0.04	1.94	36.00
37.90	0.13	32.90	22.60	73.10	0.05	236.00	0.01	0.21	140.00	3.40	0.76	60.60
14.80	0.15	7.85	7.99	25.80	0.04	166.00	0.01	1.88	76.70	0.49	1.28	70.80
31.90	0.17	6.88	11.80	53.70	0.06	104.00	0.01	0.21	229.00	0.04	1.34	64.00
30.70	0.21	72.20	12.70	48.50	0.02	119.00	0.06	1.59	40.40	0.80	0.83	32.30

1.53	0.17	6.88	12.70	86.70	0.02	28.20	0.01	1.07	65.60	0.11	1.18	12.80
42.80	0.18	109.00	38.80	116.00	0.04	254.00	0.15	1.28	254.00	4.28	1.43	87.30
30.70	0.34	84.50	19.60	48.50	0.12	97.00	0.01	3.71	47.50	1.22	1.13	97.00
402.00	0.48	155.00	147.00	127.00	0.11	4940.00	0.27	4.97	684.00	52.70	1.77	135.00
30.70	0.17	17.80	13.20	11.70	0.08	52.70	0.01	3.50	103.00	2.22	2.09	46.70
13.80	0.28	6.88	11.80	25.80	0.07	86.10	0.02	5.09	42.20	1.56	0.92	64.00
1.53	0.07	6.88	7.53	112.00	0.05	11.50	0.01	1.59	47.50	0.27	1.02	20.90
58.10	0.30	46.60	22.10	108.00	0.07	154.00	0.12	1.28	73.00	2.84	0.41	64.00
31.80	0.19	6.88	24.60	63.60	0.10	159.00	0.01	2.62	69.30	3.42	0.87	50.30
21.40	0.20	53.10	8.92	11.70	0.05	163.00	0.01	0.79	40.40	2.56	1.80	36.00
12.80	0.28	96.60	20.60	68.40	0.07	120.00	0.06	1.69	76.70	2.81	1.15	28.60
40.40	0.14	72.20	26.10	43.20	0.07	153.00	0.06	0.36	144.00	1.20	0.54	28.60
5.83	0.18	35.80	1.36	15.10	0.07	12.10	0.02	2.68	50.30	0.04	1.34	63.40
1.53	0.32	39.80	8.16	46.20	0.12	20.40	0.08	7.68	118.00	0.04	1.41	141.00
72.80	0.15	18.90	1.36	44.20	0.08	7.81	0.01	2.27	126.00	0.04	1.39	63.40
5.83	0.14	12.70	1.36	11.70	0.07	12.10	0.01	2.74	31.90	0.04	0.80	43.60
10.30	0.13	6.88	1.36	11.70	0.08	58.60	0.01	0.21	112.00	0.97	0.47	14.90
9.20	0.16	12.70	19.20	44.20	0.07	123.00	0.01	4.91	117.00	1.32	0.41	24.10
659.00	0.97	164.00	185.00	150.00	0.17	17200.00	0.28	3.26	270.00	70.40	1.95	178.00
92.60	0.17	53.40	55.00	63.80	0.09	573.00	0.09	3.41	150.00	9.01	0.10	33.80
12.50	0.08	12.70	15.30	54.20	0.06	105.00	0.01	2.14	113.00	1.49	0.80	53.50
1.53	0.14	18.90	16.50	11.70	0.05	33.40	0.01	3.86	55.40	0.25	0.81	68.40
1.53	0.20	22.20	15.30	15.10	0.08	40.00	0.02	3.36	60.50	0.63	0.87	63.40
1.53	0.05	12.70	4.53	35.70	0.04	7.81	0.01	1.17	41.20	0.34	0.62	56.00
1.53	0.06	28.90	1.36	25.70	0.05	12.10	0.01	5.70	83.10	0.54	1.27	38.70
1.75	0.06	6.88	11.50	15.10	0.06	15.30	0.01	1.07	45.10	0.30	0.52	56.00
1660.00	0.94	239.00	203.00	143.00	0.08	18100.00	0.28	0.21	182.00	170.00	1.19	153.00
19.20	0.12	46.90	39.00	35.70	0.08	281.00	0.01	3.98	110.00	4.70	0.51	58.50
23.40	0.25	18.90	23.70	63.80	0.07	91.80	0.01	1.88	76.80	3.17	0.64	53.50
1.53	0.16	6.88	6.24	25.70	0.04	17.70	0.01	0.21	37.20	0.36	1.04	43.60
756.00	0.25	185.00	207.00	136.00	0.12	6890.00	0.25	3.06	159.00	185.00	3.58	73.40
460.00	0.32	46.90	111.00	73.10	0.10	1700.00	0.10	0.21	138.00	17.90	0.43	28.90
978.00	0.57	280.00	249.00	193.00	0.11	48700.00	0.39	2.95	266.00	424.00	1.55	422.00
843.00	0.30	146.00	201.00	143.00	0.06	6510.00	0.31	3.06	190.00	152.00	3.91	93.20
3480.00	1.84	360.00	315.00	142.00	0.08	181000.00	0.54	2.62	400.00	315.00	0.66	4128.00
813.00	0.48	271.00	282.00	202.00	0.11	49000.00	0.38	2.53	310.00	232.00	0.88	670.00
1880.00	2.62	350.00	338.00	208.00	0.10	66800.00	0.57	2.21	331.00	183.00	2.63	3320.00
1100.00	0.46	425.00	318.00	208.00	0.07	51800.00	0.60	1.78	441.00	276.00	8.09	292.00
1810.00	3.80	209.00	263.00	183.00	0.13	17500.00	0.51	2.87	268.00	55.80	1.53	1710.00
658.00	0.31	251.00	205.00	150.00	0.11	10400.00	0.39	6.32	223.00	159.00	11.60	189.00
911.00	0.49	303.00	292.00	215.00	0.15	41700.00	0.48	2.38	339.00	302.00	3.46	699.00
2510.00	3.98	197.00	195.00	176.00	0.10	18100.00	0.36	4.27	192.00	74.20	0.20	4128.00
688.00	0.36	280.00	217.00	150.00	0.10	21900.00	0.37	2.39	250.00	378.00	0.33	233.00
2250.00	1.06	296.00	210.00	176.00	0.10	29300.00	0.37	2.68	292.00	138.00	0.14	697.00
1270.00	0.76	352.00	285.00	368.00	0.16	78500.00	0.43	4.52	394.00	498.00	2.60	792.00
997.00	1.07	185.00	198.00	107.00	0.09	12600.00	0.25	4.52	209.00	89.60	2.77	143.00
804.00	0.51	255.00	237.00	157.00	0.09	43000.00	0.51	4.43	367.00	449.00	1.15	93.20

Lymphotactin	MCP-1 / JE	MCP-3	MCP-5	M-CSF	MDC	MIP-1 alpha	MIP-1 beta	MIP-1gamma	MIP-2	MIP-3beta	Myoglobin	OSM	RANTES
74.00	44.30	110.00	73.20	4.96	219.00	0.10	22.70	20.70	7.31	0.12	26.10	0.02	10.80
80.00	68.70	226.00	58.80	5.28	274.00	0.15	32.80	24.20	7.31	0.41	666.00	0.02	12.00
106.00	113.00	318.00	148.00	5.55	319.00	0.14	51.30	17.30	35.10	0.43	291.00	0.02	16.60
111.00	146.00	379.00	173.00	5.82	428.00	0.10	107.00	16.50	28.90	0.36	1200.00	0.05	24.30
81.60	68.70	207.00	30.00	3.60	134.00	0.12	22.70	19.20	8.64	0.66	59.00	0.02	14.80
83.10	137.00	478.00	109.00	4.49	149.00	0.11	22.70	15.90	8.01	0.25	27.00	0.02	10.80
93.80	202.00	664.00	256.00	5.37	219.00	0.11	195.00	16.30	27.90	0.28	73.60	0.02	22.80
105.00	122.00	458.00	116.00	4.81	166.00	0.08	22.70	20.30	9.24	0.30	120.00	0.02	10.90
128.00	86.30	267.00	58.80	4.88	251.00	0.13	67.80	22.80	12.50	0.36	251.00	0.02	13.90
63.50	126.00	472.00	201.00	5.25	333.00	0.10	22.70	19.10	10.80	0.49	77.40	0.03	21.30
77.00	88.20	419.00	148.00	5.55	279.00	0.14	22.70	25.50	7.31	0.43	7.14	0.02	21.30
81.60	64.10	226.00	102.00	4.45	279.00	0.10	22.70	22.60	7.31	0.15	68.30	0.02	16.50
134.00	180.00	520.00	159.00	4.36	164.00	0.10	22.70	20.60	12.50	0.41	130.00	0.02	19.00
86.10	206.00	701.00	145.00	4.31	151.00	0.10	22.70	21.30	10.40	0.20	301.00	0.02	25.80
105.00	231.00	657.00	201.00	4.54	215.00	0.10	22.70	23.20	8.01	0.30	104.00	0.02	25.80
56.10	194.00	570.00	166.00	4.23	194.00	0.07	22.70	15.70	25.80	0.15	30.80	0.02	14.80
35.70	380.00	962.00	183.00	4.61	225.00	0.11	22.70	20.20	33.00	0.36	228.00	0.02	14.80
62.00	189.00	578.00	91.20	4.26	219.00	0.15	188.00	20.00	60.00	0.65	94.60	0.02	35.60
77.00	132.00	460.00	159.00	4.33	185.00	0.13	22.70	17.80	22.20	0.46	231.00	0.02	14.80
486.00	562.00	1410.00	420.00	5.28	473.00	0.08	75.60	55.40	41.50	0.46	118.00	0.02	58.60
89.20	632.00	1160.00	319.00	5.26	348.00	0.10	137.00	17.20	99.20	0.33	238.00	0.02	47.40
80.00	489.00	1280.00	452.00	4.82	262.00	0.15	137.00	16.20	61.10	0.16	558.00	0.02	40.20
142.00	1310.00	2340.00	329.00	4.12	189.00	0.10	216.00	29.10	48.50	0.12	98.40	0.02	32.80
148.00	3220.00	4110.00	642.00	4.39	200.00	0.08	766.00	24.20	405.00	0.20	73.80	0.18	71.70
148.00	1240.00	2730.00	375.00	4.93	202.00	0.13	302.00	24.80	243.00	0.56	131.00	0.12	43.50
86.10	2310.00	3520.00	594.00	4.14	225.00	0.14	449.00	13.90	276.00	0.25	219.00	0.24	69.40
92.20	1240.00	2670.00	464.00	4.29	172.00	0.09	115.00	22.00	194.00	0.22	36.20	0.03	39.60
206.00	2970.00	2170.00	505.00	4.62	168.00	0.18	759.00	31.00	267.00	0.60	339.00	0.17	40.20
123.00	821.00	2000.00	666.00	4.85	234.00	0.13	152.00	29.40	87.30	0.25	37.10	0.02	46.10
242.00	3500.00	3130.00	1040.00	5.77	350.00	0.15	1150.00	45.20	719.00	0.65	348.00	0.24	75.20
210.00	8230.00	4150.00	1360.00	5.82	489.00	0.12	1220.00	31.10	1840.00	0.25	1160.00	0.63	87.60
187.00	2630.00	1550.00	517.00	5.04	283.00	0.17	862.00	43.10	307.00	0.72	48.90	0.21	60.40
136.00	733.00	1460.00	666.00	4.54	622.00	0.16	340.00	40.00	238.00	0.30	318.00	0.02	78.60
77.00	322.00	891.00	375.00	4.57	302.00	0.12	145.00	25.70	89.00	0.30	96.80	0.02	40.20
112.00	1040.00	1900.00	618.00	4.22	424.00	0.15	407.00	22.10	494.00	0.28	132.00	0.02	54.30
89.20	942.00	902.00	433.00	4.56	289.00	0.12	230.00	28.10	50.10	0.65	605.00	0.05	38.20
80.00	452.00	1170.00	439.00	4.78	333.00	0.16	296.00	32.00	211.00	0.33	203.00	0.02	58.80
153.00	1710.00	3050.00	992.00	4.63	903.00	0.20	572.00	54.90	199.00	0.58	124.00	0.10	113.00
89.20	296.00	1030.00	356.00	4.08	397.00	0.10	22.70	40.60	11.50	0.77	123.00	0.02	41.50
99.90	421.00	1190.00	483.00	5.22	529.00	0.09	75.60	33.00	91.30	0.33	177.00	0.05	32.80
59.00	427.00	1000.00	352.00	4.84	463.00	0.16	22.70	45.90	184.00	0.60	40.60	0.02	62.20
105.00	225.00	675.00	239.00	4.75	407.00	0.14	22.70	35.70	21.70	0.26	727.00	0.02	27.20
156.00	2310.00	3870.00	837.00	4.80	369.00	0.09	498.00	41.20	146.00	0.41	118.00	0.11	58.60
86.10	785.00	1990.00	471.00	4.62	325.00	0.14	22.70	40.00	56.70	0.49	65.40	0.02	44.80
114.00	830.00	1950.00	458.00	4.37	298.00	0.11	22.70	41.50	33.00	0.41	92.40	0.02	32.10
95.30	1300.00	2760.00	452.00	4.01	249.00	0.16	22.70	28.80	26.80	0.12	140.00	0.02	40.20

105.00	1650.00	2970.00	986.00	4.47	412.00	0.09	51.30	24.20	69.90	0.25	696.00	0.02	57.40
195.00	4810.00	6470.00	1890.00	5.65	697.00	0.11	805.00	33.60	353.00	0.56	660.00	0.29	113.00
63.50	449.00	921.00	356.00	4.93	475.00	0.15	195.00	35.00	69.90	0.58	23.60	0.02	37.60
259.00	2530.00	5180.00	1550.00	9.27	1410.00	0.24	3410.00	157.00	4450.00	1.01	231.00	0.49	203.00
81.60	1140.00	1620.00	794.00	6.20	600.00	0.12	209.00	25.10	169.00	0.20	347.00	0.02	32.80
59.00	1230.00	1260.00	733.00	5.68	643.00	0.13	425.00	20.00	422.00	0.22	599.00	0.13	28.60
105.00	660.00	659.00	375.00	5.07	436.00	0.10	137.00	14.40	198.00	0.20	646.00	0.02	39.60
77.00	2850.00	3990.00	1350.00	4.21	430.00	0.13	460.00	18.20	604.00	0.41	1010.00	0.28	51.10
114.00	2450.00	4260.00	1170.00	4.80	346.00	0.13	195.00	21.90	190.00	0.08	91.70	0.10	56.10
57.50	843.00	1920.00	445.00	4.41	296.00	0.11	22.70	26.10	60.00	0.25	289.00	0.02	26.50
92.20	1820.00	3330.00	704.00	5.12	360.00	0.13	160.00	28.20	113.00	0.38	230.00	0.06	42.80
130.00	3350.00	5370.00	1520.00	5.25	436.00	0.13	395.00	28.70	69.90	0.15	730.00	0.14	64.60
92.40	385.00	490.00	262.00	5.50	580.00	0.10	97.90	13.90	31.60	0.30	465.00	0.07	51.30
190.00	367.00	505.00	307.00	6.18	554.00	0.24	200.00	15.70	33.10	1.12	360.00	0.02	43.40
107.00	137.00	284.00	67.80	4.01	175.00	0.06	22.70	21.70	7.31	0.37	144.00	0.02	10.90
44.50	265.00	515.00	242.00	4.29	424.00	0.13	22.70	16.50	19.20	0.23	862.00	0.02	34.80
100.00	726.00	1300.00	264.00	4.26	291.00	0.15	22.70	33.70	30.80	0.21	676.00	0.02	36.20
114.00	2290.00	3710.00	971.00	5.69	396.00	0.14	231.00	24.40	147.00	0.32	2400.00	0.07	52.60
263.00	13200.00	13500.00	1970.00	5.79	683.00	5.35	84600.00	37.30	11400.00	0.16	529.00	0.77	468.00
230.00	4250.00	4800.00	1910.00	6.12	499.00	0.26	1480.00	42.60	1330.00	0.54	250.00	0.23	103.00
80.20	1040.00	1810.00	602.00	4.95	252.00	0.06	58.50	20.20	37.10	0.21	450.00	0.02	37.70
108.00	1220.00	1190.00	576.00	5.40	403.00	0.14	152.00	17.90	106.00	0.32	523.00	0.02	34.80
132.00	680.00	1060.00	402.00	6.03	424.00	0.06	97.90	24.80	65.90	0.36	1200.00	0.02	39.10
138.00	357.00	612.00	276.00	4.64	298.00	0.15	84.90	18.90	44.30	0.17	363.00	0.02	24.10
124.00	360.00	503.00	286.00	5.12	301.00	0.08	49.40	20.50	30.80	0.27	52.40	0.02	27.30
100.00	368.00	609.00	186.00	5.14	308.00	0.07	71.80	23.90	23.30	0.21	272.00	0.02	32.60
240.00	17600.00	16700.00	2730.00	3.46	751.00	4.53	61800.00	26.00	22100.00	0.17	593.00	0.97	470.00
155.00	3210.00	3880.00	1170.00	4.84	418.00	0.13	432.00	21.20	826.00	0.45	1060.00	0.14	81.90
103.00	1610.00	2220.00	717.00	5.37	332.00	0.12	226.00	24.50	93.90	0.21	197.00	0.04	56.50
78.80	608.00	1220.00	295.00	4.23	163.00	0.05	22.70	17.50	7.31	0.21	550.00	0.02	28.00
228.00	11500.00	18200.00	3280.00	3.49	464.00	3.15	22600.00	24.60	29600.00	0.39	93.90	0.70	447.00
111.00	3050.00	3150.00	1090.00	3.18	367.00	0.75	6370.00	46.70	2890.00	0.48	121.00	0.25	272.00
336.00	34700.00	54200.00	4430.00	6.36	874.00	1.25	6840.00	70.70	62000.00	0.32	526.00	1.01	435.00
259.00	10400.00	14700.00	3740.00	3.94	589.00	3.21	25200.00	28.90	20900.00	0.17	94.30	0.79	507.00
344.00	32900.00	36700.00	3690.00	8.42	924.00	3.36	14200.00	60.10	70200.00	0.36	1340.00	1.35	403.00
312.00	16300.00	26500.00	2700.00	7.82	952.00	0.30	3020.00	74.00	36800.00	0.41	1580.00	0.95	319.00
352.00	34500.00	30500.00	3370.00	6.57	618.00	25.60	59300.00	39.00	105000.00	0.25	4010.00	1.59	464.00
405.00	43600.00	65400.00	3590.00	5.88	832.00	5.65	28900.00	100.00	33100.00	0.51	31.70	1.31	547.00
327.00	7870.00	5260.00	1200.00	7.25	712.00	3.93	5200.00	12.60	36600.00	0.60	1170.00	1.11	330.00
312.00	12400.00	26300.00	1780.00	6.72	556.00	0.25	1770.00	72.70	13800.00	0.51	454.00	0.99	257.00
406.00	23000.00	39200.00	5170.00	9.37	962.00	0.72	5800.00	103.00	19900.00	0.70	2360.00	1.06	472.00
286.00	17100.00	6520.00	749.00	6.84	172.00	1.36	2300.00	13.60	37200.00	0.42	532.00	0.80	314.00
325.00	25000.00	44700.00	3420.00	8.09	1030.00	0.40	3800.00	74.30	32100.00	0.39	331.00	0.85	388.00
357.00	42400.00	32000.00	4350.00	6.43	852.00	1.85	21300.00	28.40	19900.00	0.32	442.00	1.10	476.00
393.00	23400.00	33000.00	3290.00	7.37	940.00	2.03	11800.00	84.80	79300.00	0.39	565.00	1.02	538.00
284.00	9090.00	11500.00	2560.00	4.82	689.00	9.71	62800.00	34.20	16900.00	0.29	193.00	0.80	455.00
372.00	29900.00	51500.00	5590.00	4.99	587.00	2.42	8620.00	30.50	55700.00	0.51	105.00	1.01	441.00

SCF	SGOT	TIMP-1	TF	TNF-alpha	TPO	VCAM-1	VEGF	vWF
40.50	14.80	3.85	0.42	0.02	5.42	1630.00	107.00	21.20
38.50	15.30	2.63	1.02	0.07	8.73	1580.00	180.00	20.30
89.50	5.76	4.57	0.89	0.02	13.10	1390.00	166.00	28.00
104.00	6.23	2.55	3.21	0.10	17.10	1510.00	150.00	8.00
17.00	15.80	1.02	0.95	0.04	8.54	1230.00	129.00	12.50
54.70	14.20	1.13	1.47	0.13	8.17	1110.00	55.70	26.50
102.00	8.87	2.90	0.95	0.07	7.60	1120.00	145.00	33.20
50.50	12.50	1.79	0.39	0.02	5.42	1210.00	107.00	22.20
63.20	13.80	5.20	0.45	0.06	7.60	1500.00	102.00	20.80
50.50	11.00	3.84	1.02	0.07	7.41	1620.00	139.00	25.10
54.70	12.30	6.17	0.92	0.03	7.02	1560.00	107.00	24.10
40.50	14.80	2.31	0.63	0.02	6.23	1640.00	134.00	23.20
80.90	12.90	1.85	0.76	0.02	6.03	1230.00	118.00	34.70
61.00	14.70	1.80	1.09	0.02	7.02	1250.00	110.00	22.70
54.70	14.40	2.06	0.34	0.15	5.42	1360.00	88.40	21.20
42.40	9.72	1.10	0.39	0.02	7.02	987.00	76.10	20.30
46.40	15.20	2.95	0.82	0.02	7.70	1390.00	118.00	20.80
54.70	15.30	4.15	1.15	0.02	12.60	1370.00	131.00	19.30
50.50	16.40	2.67	0.57	0.07	7.41	1490.00	145.00	24.60
23.80	17.60	16.40	0.34	0.06	7.89	2160.00	177.00	17.40
80.90	6.51	4.00	1.65	0.06	12.30	1370.00	145.00	28.50
85.50	8.79	2.89	1.15	0.15	10.90	1120.00	76.10	15.90
54.70	15.30	4.00	0.57	0.07	6.23	1240.00	129.00	15.40
119.00	15.00	5.26	0.39	0.19	6.53	1240.00	194.00	26.50
131.00	8.16	4.44	1.05	0.10	10.00	921.00	169.00	34.70
90.10	10.10	2.82	1.02	0.19	9.65	879.00	153.00	37.50
58.90	12.40	3.13	0.63	0.06	8.64	1110.00	113.00	28.90
109.00	15.60	5.60	0.63	0.21	6.23	1250.00	221.00	21.20
54.70	11.80	4.05	0.57	0.09	7.22	1490.00	194.00	38.00
159.00	12.50	6.84	1.15	0.25	12.80	1520.00	322.00	28.90
258.00	6.53	6.09	0.95	0.42	12.20	1540.00	361.00	29.90
124.00	17.10	5.10	1.09	0.09	8.73	1590.00	233.00	31.80
99.50	12.90	18.00	1.79	0.18	10.80	2160.00	177.00	28.90
44.40	14.80	8.54	0.57	0.02	10.50	1530.00	156.00	21.20
107.00	9.43	10.20	1.76	0.15	15.60	1490.00	199.00	33.70
50.50	15.20	6.38	0.69	0.04	7.98	1700.00	123.00	30.80
67.50	11.10	14.80	1.29	0.06	12.20	1650.00	183.00	21.20
124.00	12.70	33.10	2.24	0.18	13.80	1780.00	249.00	30.80
7.78	20.30	9.54	1.29	0.02	7.02	1840.00	63.30	20.30
76.40	10.80	10.40	1.68	0.03	12.70	1620.00	150.00	45.00
32.80	18.90	11.10	1.65	0.02	13.70	1570.00	102.00	31.30
54.70	12.20	6.45	1.58	0.02	12.60	1700.00	118.00	7.50
65.30	15.50	11.40	0.76	0.13	9.28	1380.00	227.00	27.00
34.70	18.00	8.22	0.89	0.07	10.40	1190.00	134.00	22.20
27.30	18.40	6.97	0.45	0.02	6.83	1330.00	123.00	21.20
50.50	16.40	7.35	0.23	0.02	7.98	1050.00	123.00	27.00

80.90	6.50	5.24	0.39	0.03	7.50	1180.00	150.00	49.30
193.00	4.97	17.30	0.76	0.19	12.70	1360.00	339.00	70.20
34.70	16.30	10.10	1.12	0.02	11.10	1410.00	134.00	36.60
389.00	5.19	32.90	1.79	0.63	19.80	2860.00	550.00	77.60
87.80	5.74	9.21	1.51	0.04	12.50	1510.00	172.00	68.40
121.00	5.35	6.84	1.22	0.07	13.00	1350.00	134.00	78.10
76.40	6.07	3.41	0.69	0.04	10.70	1270.00	131.00	43.20
188.00	5.86	11.20	1.87	0.20	13.50	676.00	221.00	50.70
149.00	8.67	12.30	1.15	0.10	13.30	895.00	131.00	35.60
38.50	13.60	6.32	0.76	0.13	8.45	1100.00	102.00	28.00
107.00	10.20	8.47	1.09	0.18	10.40	1090.00	172.00	40.30
94.80	11.30	11.90	0.76	0.15	7.98	1410.00	188.00	37.50
84.30	5.13	3.48	1.54	0.06	7.63	1580.00	141.00	45.50
118.00	4.59	3.38	2.97	0.23	12.60	1420.00	219.00	97.40
6.81	17.40	2.94	0.56	0.02	5.98	1730.00	99.50	20.10
32.90	10.80	4.38	1.14	0.02	7.41	1510.00	108.00	26.00
22.10	17.40	4.83	1.31	0.03	7.41	1520.00	126.00	17.70
127.00	9.47	7.45	1.65	0.13	9.09	1640.00	200.00	31.50
381.00	8.08	283.00	2.30	1.10	15.60	1760.00	858.00	46.30
152.00	12.10	12.40	1.68	0.30	13.20	2110.00	302.00	21.30
55.10	14.60	7.56	1.42	0.04	7.20	1550.00	143.00	22.90
63.60	8.96	4.96	1.25	0.09	7.84	1700.00	141.00	33.80
59.40	10.40	7.09	1.59	0.09	6.84	2650.00	136.00	18.90
53.30	13.20	3.54	1.20	0.08	5.96	2020.00	101.00	19.30
63.60	14.20	3.13	0.59	0.04	5.05	2000.00	112.00	25.20
36.20	14.40	5.83	0.83	0.06	6.40	2110.00	146.00	20.50
397.00	10.90	282.00	1.87	1.03	16.20	1050.00	688.00	34.20
132.00	7.85	9.11	1.45	0.18	14.00	1420.00	239.00	36.20
88.50	12.80	5.70	1.31	0.09	10.20	1620.00	170.00	29.90
39.50	18.00	4.66	1.02	0.02	5.51	1420.00	92.60	15.70
418.00	5.25	107.00	1.34	0.87	12.70	1090.00	651.00	67.40
154.00	15.50	26.40	1.87	0.38	12.40	1270.00	307.00	21.30
628.00	2.39	98.50	2.00	1.42	17.70	1350.00	978.00	88.80
388.00	4.37	98.90	1.57	0.97	13.50	1060.00	640.00	88.00
722.00	0.19	308.00	1.15	2.19	14.10	1070.00	2590.00	126.00
601.00	0.26	166.00	1.72	1.36	20.40	1400.00	824.00	119.00
756.00	0.19	358.00	0.95	1.50	13.10	649.00	3410.00	53.50
785.00	5.71	140.00	2.53	1.83	20.20	1090.00	1220.00	67.90
437.00	0.19	131.00	1.58	0.66	16.10	704.00	2370.00	15.40
486.00	0.19	66.50	2.01	1.01	19.40	886.00	452.00	139.00
781.00	2.53	164.00	2.16	2.24	20.80	1980.00	980.00	140.00
399.00	0.19	117.00	2.00	0.75	14.80	273.00	1360.00	6.23
557.00	2.10	107.00	1.31	1.27	17.20	1590.00	735.00	89.60
598.00	3.02	154.00	1.70	1.14	11.30	1160.00	907.00	47.80
783.00	3.39	247.00	2.14	1.84	16.00	2080.00	1570.00	67.40
418.00	5.97	297.00	1.76	1.17	14.60	1450.00	1020.00	57.20
743.00	3.62	85.00	1.37	2.19	16.20	1500.00	1000.00	72.20